**Name of Journal: *World Journal of Gastrointestinal Pharmacology and Therapeutics***

**ESPS Manuscript NO: 18903**

**Manuscript type: REVIEW**

**Diagnosis and management of functional symptoms in inflammatory bowel disease in remission**

Teruel C *et al*. IBS symptoms in quiescent IBD

**Carlos Teruel, Elena Garrido, Francisco Mesonero**

**Carlos Teruel, Elena Garrido, Francisco Mesonero,** Gastroenterology Department, Hospital Ramón y Cajal, 28034 Madrid, Spain

**Author contributions**: All authors contributed equally to this work.

**Conflicts-of-interest statement:** The authors declare no conflicts of interest.

**Open-access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC-BY-NC-4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to:** **Carlos Teruel, MD**, Gastroenterology Department, Hospital Ramón y Cajal, Ctra. Colmenar Viejo; km. 9100, 28034 Madrid, Spain. cteruelvegazo@yahoo.es

**Telephone:** +34-91-3368354

**Fax:** +34-91-3368354

**Received:** April 28, 2015

**Peer-review started:** May 6, 2015

**First decision:** July 17, 2015

**Revised:** September 3, 2015

**Accepted:** October 20, 2015

**Article in press:**

**Published online:**

**Abstract**

Inflammatory bowel disease (IBD) patients in remission may suffer from gastrointestinal symptoms that resemble irritable bowel syndrome (IBS). Knowledge on this issue has increased considerably in the last decade, and it is our intention to review and summarize it in the present work. We describe a problematic that comprises physiopathological uncertainties, diagnostic difficulties, as IBS-like symptoms are very similar to those produced by an inflammatory flare, and the necessity of appropriate management of these patients, who, although in remission, have impaired quality of life. Ultimately, from almost a philosophical point of view, the presence of IBS-like symptoms in IBD patients in remission supposes a challenge to the traditional functional-organic dichotomy, suggesting the need for a change of paradigm.

**Key words:** Inflammatory bowel disease; Crohn’s disease; Ulcerative colitis; Irritable bowel syndrome; Functional gastrointestinal disease

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Many inflammatory bowel disease patients in remission suffer from ongoing gastrointestinal symptoms that resemble those of irritable bowel syndrome and that hinder their quality of life. We review the pathogenesis of these symptoms, their prevalence and the best management strategies.

Teruel C, Garrido E, Mesonero F. Diagnosis and management of functional symptoms in inflammatory bowel disease in remission. *World J Gastrointest Pharmacol Ther* 2015; In press

**INTRODUCTION**

More than thirty years ago, in 1983, it was first reported that a significant proportion of patients with inflammatory bowel disease (IBD) with normal mucosa in endoscopic examination nevertheless suffered from gastrointestinal symptoms allegedly of functional origin[1]. Almost twenty years passed until the next significant investigation addressing this issue was published, in 2002 by Simren *et al*[2]. From that year on, an important number of studies have been published providing a more profound knowledge about functional symptoms in IBD in remission. It is our objective in the present work to review this knowledge.

Within functional digestive disorders, we will focus on irritable bowel syndrome (IBS) because its symptoms (abdominal pain, diarrhea, constipation, fecal incontinence) resemble those of flare-up of IBD. Differential diagnosis between IBD flare and IBS-like symptoms is a diagnostic challenge with critical consequences. Immunomodulators could be prescribed unnecessarily or ongoing inflammation managed inadequately with, for example, antispasmodics, delaying initiation of proper treatment when not resulting in adverse events.

Some authors have explored the prevalence of IBS symptoms in active IBD[3-5]. We consider, as many others, that it is very difficult to discriminate reliably symptoms attributable to IBD from those secondary to a functional disorder in that setting, so we will not explore this aspect further.

Increasing knowledge about the occurrence of IBS symptoms in IBD patients with no macroscopic inflammation, has led to the definition of so-called “IBD-IBS”. This concept, together with further awareness of links between the two entities, challenges the traditional functional-organic dichotomy and leads to the elaboration of a broader biopsychosocial model of disease that should allow a better understanding of patients´ medical condition that the classical dogma fails to achieve[6-8].

We have structured the review following a question-and-answer scheme with intent to reproduce what comes into mind of the physician in the outpatient clinic. Key conclusions in each section are presented.

**HOW DO I KNOW THAT IBD IS IN REMISSION?**

To confidently define remission non-invasively we should use not only clinical indexes but also C-reactive protein and fecal calprotectin. Radiological procedures could be of help in unclear cases. Endoscopy would still be necessary to confirm remission in many cases.

The definition of remission in IBD is not straight-forward, as it is a broad concept that includes several aspects: (1) clinical remission (absence of symptoms); (2) endoscopic remission (mucosal healing); and (3) deep remission (no symptoms and mucosal healing).

To enhance the optimal diagnosis of remission several indices are available to monitor IBD inflammatory activity, such as the Crohn´s Disease Activity Index (CDAI) or the Harvey-Bradshaw index for Crohn´s Disease (CD), or the Mayo score for ulcerative colitis (UC). They are a composite of objective items (such as analytical determinations), objective items self-reported by the patient (such as number of stools per day) and purely subjective items such as pain intensity or degree of wellbeing. Although valuable in monitoring disease progression and activity[9] and therefore widely used in clinical trials, these indices do not correlate perfectly with endoscopic/histological activity or analytical parameters, probably because they all include subjective items[10-12]. Sub-analyses of some recent clinical trials show that up to 18% of randomized patients, all with scores in the range of active disease as defined in the inclusion criteria, actually had no evidence of endoscopic inflammation[13]. Lahiff *et al*[10] measured CDAI in 44 CD patients and in 47 IBS patients, and noticed that 62% of IBS patients had a score higher than 150 (the usual threshold for inclusion in IBD clinical trials) and that mean scores were higher in IBS patients (183 points versus 157, *P* < 0.05). More intense pain and worse perception of general wellbeing were the main contributors to the final score in IBS. Authors conclude that remission cannot be determined solely on clinical indices, as their subjective components makes it impossible to separate functional from inflammatory symptoms[10,14].

According to all this, additional tools are needed to establish a reliable diagnosis of remission in IBD[15]: (1) Endoscopic examination of the intestinal mucosa is the gold standard to determine inflammatory activity and the most reliable test to define remission. However, endoscopy is invasive and uncomfortable, not devoid of side effects. Moreover, there are no clear or widely accepted criteria of endoscopic remission. On top of that, small bowel inflammatory activity can be very difficult to evaluate, even though the availability of the endoscopic capsule has increased in recent years; (2) Radiological imaging in IBD has lately experienced great advances. Ultrasound, computerized tomography (CT) and magnetic resonance imaging (MRI) are no longer used solely to rule out complications such as abscesses or perforation. They all play an increasing role in assessing the extent of disease, presence of active inflammation, transmural involvement and even response to treatment, all of which are especially true for MRI[16]; (3) C-reactive Protein (CRP) is the best serum marker of inflammatory activity in IBD, and reliably predicts treatment response[17,18]. It is therefore widely used in clinical practice. CRP is however an unspecific acute phase reactant, and up to 25% of patients with inflammatory activity will have normal levels[19,20]; and (4) Determination of fecal markers of neutrophilic activity in intestinal mucosa is a simple tool that reliably predicts the presence of significant mucosal inflammation[21,22]. Calprotectin is the most used marker and has excellent diagnostic performance. In a meta-analysis the area under the receiver operating characteristic (ROC) curve was 0.97, with an optimal cut-off value of 50 mcg/g that yielded 93% sensitivity and 94% specificity in discriminating IBD from IBS[22]. Further on, calprotectin levels correlate very well with endoscopic activity[23-27], predict occurrence of a flare[28] and are capable of predicting response to treatment[27,29-31]. However, calprotectin also rises in other situations, such as with non-steroidal anti-inflammatory drugs (NSAIDs) use, and we lack a cut-off point that defines remission reliably[32]. As we describe in detail later, measurement of fecal calprotectin in IBD patients in remission could determine if the presence of symptoms is due to true functional syndromes or to ongoing inflammation[5,33-35].

**ARE ALL PATIENTS IN REMISSION SUSCEPTIBLE TO SUFFERING IBS-LIKE SYMPTOMS?**

Some IBD patients have risk factors for developing conditions such as bile salt diarrhea that can mimic IBS-like symptoms.

IBD patients in remission with previous intestinal surgery, stenosis or stomas are at risk of developing small intestine bacterial overgrowth (SIBO), subocclusive crisis or bile acid malabsorption. These three conditions cause symptoms that resemble IBS. Many authors exclude such patients when considering IBD-IBS prevalence, but others do not (Table 1). None have systematically carried out tests to rule out such conditions before definitive diagnosis, such as breath tests, enteroclysis, or a SeHCAT [tauroselcholic (75 selenium) acid] test respectively. Before establishing a purely functional nature of symptoms, it seems reasonable to consider such tests in IBD patients at risk of suffering these conditions or to carry out an empirical therapeutic trial for example with non-absorbable antibiotics or cholestyramine.

**WHICH CRITERIA ARE VALID TO DIAGNOSE FUNCTIONAL SYMPTOMS IN IBD PATIENTS?**

In absence of better alternatives, Rome III criteria can be used to diagnose IBS in IBD patients in remission.

Irritable bowel syndrome is defined by the presence of abdominal pain or discomfort associated with changes in stool frequency or consistency. To date there is no biomarker available that can reliably confirm or exclude it. It is therefore a clinical diagnosis based on exclusion of organic disease in the presence of alarm symptoms (weight loss, anemia, gastrointestinal bleeding, *etc.*) and fulfillment of predefined criteria. Currently Rome III criteria are without a doubt the most used to define IBS in epidemiological studies, clinical trials and everyday practice (Table 2)[39-41].

There are no consensus definitions for diagnosis of IBS-like symptoms in quiescent IBD. In general, investigators have used diagnostic criteria that were validated in non-IBD patients (Table 1). In 2005 Barratt *et al*[42] observed that several symptoms were more frequent when their etiology was functional and not inflammatory (exclusively daytime symptoms, bloating, excess gas, fatigue). They elaborated the St Marks Dairy Score, a tool to diagnose IBS-like symptoms in quiescent IBD. However, this score has not been validated externally to date.

**HOW MANY IBD PATIENTS IN REMISSION HAVE IBS-LIKE SYMPTOMS?**

IBD-IBS prevalence data are very variable due to heterogeneity in remission definition, diagnostic criteria and exclusion criteria. Pooling prevalences of the most homogeneous studies shows that about a third of quiescent IBD patients will suffer from IBS-like symptoms.

From 1983 until 2014 a total of 19 studies have measured the prevalence of IBS-like symptoms in IBD[1-5,33-35,42-52]. Two of these publications refer to the same IBD cohort[34,49], leaving 18 prevalence estimations. Two studies explore IBS symptoms in IBD patients regardless their inflammatory activity status[42,47]. The 16 remaining studies are summarized in Table 1. Three studies report IBS-like prevalences in both active and quiescent IBD[3-5]; from these studies we have extracted only data referring to IBD in remission. There are 10 cross-sectional studies, one prospective study (patients are followed systematically and in each visit they are assessed for presence of IBS-like symptoms) and 5 are case-control studies in which IBS-like symptoms prevalence in IBD patients is compared to IBS prevalence in non-IBD patients. Fourteen studies use the Rome criteria for IBS diagnosis (6 Rome II, 6 Rome III, one both and another Rome II and Manning criteria), one uses Manning criteria only[1,53] and the last one uses a validated gastrointestinal symptom questionnaire[2].

The range of reported prevalences is quite wide (11%-64%), also in CD (12%-68%) and in UC (9%-60%) separately. Pooled prevalence is 30.9%, 38.1% in CD and 27.8% in UC (Table 1). These differences in prevalence were not attributable to type of diagnostic criteria used, as a meta-analysis by Halpin *et al*[54] that analyzed the studies published up to 2012 concludes. Possible alternative explanations are the small sample size of many of the studies, the variability in diagnostic criteria used to define IBD remission, the variability of exclusion criteria, and the absence of controls in most of them.

With respect to definitions of remission there are few coincidences between the different studies, ranging from simple clinical assessment[43,45] to a well-defined combination of IBD activity indexes and C reactive protein (CRP) quantification[5,33,48,51]. Strikingly only 7 studies include endoscopic evaluation to define remission[1,2,4,35,46,48,51]. Of those, some allow a low grade of inflammation[1,46] and only four use endoscopic indexes[35,46,48,51]. The prevalence variability seems greater in those studies without endoscopic criteria in remission definition (11.2%-63.6%) than in those with (12.9%-46%). In the five studies that included only patients with normal-appearing mucosa, variability persisted (range 12.9%-45.7%).

Regarding variability in exclusion criteria, it is interesting to focus on the six studies that exclude patients with previous abdominal surgery (mainly in CD cohorts) to reduce confusion and bias (see previous sections)[2,5,48,50-52]. In these studies, which include a total of 719 patients (310 CD, 409 UC), the prevalence range is narrower but still considerable and still greater in CD: range 32%-44.6% for all patients, 35.4%-57% in CD and 26.7%-38% in UC.

All five case-control studies reported a higher prevalence of IBS-like symptoms in IBD patients in remission than in non-IBD controls. The meta-analysis by Halpin *et al*[54] calculated for IBD as a whole an OR of 4.39 (95%CI: 2.24-8.61). In the study by Fukuba *et al*[52], not included in the meta-analysis, the numbers were similar for UC (OR = 7.17; 95%CI: 3.94-13.0).

Some studies have investigated if there are any variables associated with the occurrence of IBS-like symptoms. Although the conclusions are hampered by small sample size of many of them, these are the main results: (1) Gender: two studies report that women have a higher risk of suffering IBS-like symptoms while in remission, as happens in conventional IBS[4,5]; another study reports a higher risk in men[46]; (2) Age: leaving aside the study by Farrokhyar *et al*[45] that reported a higher risk for patients over 40 years of age (OR = 3.2) most studies have failed to show an association between age and risk of suffering IBS-like symptoms while in remission; (3) Extension and/or location of IBD: two studies analyzed this variable and did not find a significant association with the prevalence of functional symptoms[5,33]; (4) IBD duration: only analyzed in one study with a small sample size, no significant association was found[2]; and (5) Previous surgery: analyzed only in three studies, pooled prevalence of functional symptoms was higher in operated patients [60% *vs* 32.4%)[2,30,41].

**IF THEY ARE IN REMISSION, WHY DO THEY HAVE SYMPTOMS?**

Several pathogenic mechanisms can explain the occurrence of IBD-IBS beyond a merely random effect. Dysmotility, visceral hypersensitivity and increased mucosal permeability are the best studied ones.

Several studies have investigated why some IBD patients in remission remain asymptomatic while others experience ongoing symptoms of functional origin. We summarize the different explanations that have been considered.

***It is just a random effect***

IBS is one of the most frequent gastrointestinal diseases worldwide, with a prevalence that ranges from 10% to 15% of the general population[55-58]. A similar prevalence in quiescent IBD patients would be expected. However, as we have described in the previous section, prevalence of IBD-IBS is more than double[54]. It is therefore obvious that there must be further reasons other than merely chance that explain the occurrence of IBS symptoms in IBD.

***Inflammation persists***

Microscopic inflammation in normal-appearing mucosa could persist after resolution of an acute flare and justify persistence of symptoms in spite of mucosal healing[59,60].

In 2010 Keohane *et al*[33] analyzed 106 IBD patients in remission, all with normal CRP levels, and found significantly higher fecal calprotectin levels in patients with functional symptoms than in asymptomatic patients (414.7 mg/kg *vs* 174.9 mg/kg in CD patients, 591.1 mg/kg *vs* 229.8 mg/kg in UC). They concluded against a real overlap between IBD and IBS, as persistence of symptoms would be provoked by inflammation persistence (“IBD is IBD unless proven otherwise”). It should be highlighted however, that they did not perform endoscopy systematically, so active inflammation could not be ruled out completely. Along the same lines, the work of Vivinus-Nebot *et al*[51] reported that symptomatic patients had higher levels of tumor necrotic factor alpha (TNF-α), as well as a trend towards a higher amount of intraepithelial lymphocytes and eosinophils. These studies imply that these patients could theoretically be candidates for IBD treatment escalation, a hypothesis neither proven nor tested to date.

Against this perspective several publications appeared in the following years reporting a considerable proportion of symptomatic patients with normal levels of fecal calprotectin[5,35,61], which means that there must be additional pathogenic factors and that treatment escalation in these patients should be considered very carefully, if at all.

***IBD induces dysmotility***

Several studies have detected similar colonic motility patterns in quiescent IBD than those described in IBS (higher number of low-amplitude propagated contractions)[62-64]. Subtle changes in antroduodenal motility in quiescent CD have also been described[65]. These alterations in intestinal motility could be related to autonomic nerve system dysfunction that has been described in IBD patients in remission[66-69].

***IBD induces hypersensitivity***

Several experiments with rectal balloon distension showed initially that IBD patients in remission had higher visceral pain thresholds (i.e., tolerance to pain was higher) than IBS patients[70,71]. Cerebral activity induced by peripheral stimuli in quiescent CU patients resembled more that of healthy population than the one of IBS patients[72]. IBD patients would therefore have reduced visceral sensitivity, which could be interpreted as an adaptive response in the context of chronic-recurrent inflammation.

However, when visceral sensitivity in IBD patients in remission has been studied based on the presence or absence of functional symptoms, findings have been different. A study in pediatric IBD patients in remission with residual abdominal pain observed that they presented rectal pain thresholds lower than those of healthy volunteers and similar to those of patients with functional digestive diseases[73]. Further on, two studies measured in rectosigmoid junction biopsies the density of nerve fibers that presented the transient potential vanilloid receptor type 1 (TRPV1), implicated in nociception and in IBS visceral hypersensitivity[74,75]. They observed that in symptomatic IBD patients in remission the density was significantly higher than in healthy controls and in asymptomatic IBD patients. Additionally, the number of TRPV1 fibers was proportional to pain intensity referred by the patient. IBD-IBS patients would therefore have hypersensitivity induced by up-regulation of TRPV1, which could in turn be mediated by central generated stimuli. Mast cells, which participate in the generation of abdominal pain in IBS[76,77], have also been involved in pain generation in IBS-IBD[78]. At the molecular level, it has been described additionally an up-regulation of serotonin synthesis, a well-known mediator in visceral motility and sensitivity[79].

***IBD induces mucosal permeability increment***

In IBS, intestinal permeability is constantly increased and is proportional to symptom intensity[51,80]. This phenomenon would increase mucosal exposure to endoluminal antigens that could in turn induce inflammatory, sensitive or motor responses responsible for patients´ symptoms. In IBD in remission similar findings have been reported: permeability is higher than that of healthy volunteers and is even higher in symptomatic patients[51,81]. The permeability increment has been also related to the risk of suffering a relapse[82,83].

***Microbiota disturbance plays a role***

Composition of the gut flora is disturbed in both IBS and IBD, although it is not really established whether it is a cause or a consequence of the physiological alterations that characterize such entities or of the treatments patients receive[84-86]. No studies have explored flora composition in IBD-IBS patients or compared it with asymptomatic IBD patients in remission.

***Similarities with post-infectious IBS***

After acute gastroenteritis odds of developing IBS are increased 6-7 fold[87,88]. This post-infectious IBS (PI-IBS) is conceptually very similar to IBS in quiescent IBD, as both would be caused by post-inflammatory mechanisms. Although dysmotility and hypersensitivity do not seem to explain the development of symptoms after the infection[89], mast cells and increased intestinal permeability have been involved as in IBD-IBS[7,90].

***Psychological stress: pivotal role as well?***

Specific role of psychological distress in pathogenesis of IBS symptoms in quiescent IBD remains to our knowledge uninvestigated. Evidence from its implication in IBS pathogenesis (both PI-IBS and conventional IBS)[89,91] and in IBD flare induction[92] makes it highly possible, in our opinion, that an important link exists with IBS-IBD.

**I HAVE ACHIEVED REMISSION IN MY PATIENT. WHY SHOULD I CONTINUE TO BE CONCERNED?**

In spite of being in remission, IBD-IBS patients have an impaired quality of life, and deserve attention and care.

IBD patients in general have a worse quality of life (QoL) than controls, mostly related to disease activity[93-95]. Even though quiescent IBD patients with IBS-like symptoms are not at risk of suffering direct complications of IBD such as perforations, abscesses or toxic megacolon, their symptoms can be very intense and significantly reduce their QoL, maybe as much as an actual flare does. In Table 3 we summarize all studies that have analyzed the effect of IBS-like symptom occurrence in different QoL scores and in anxiety and depression scales[2-5,33,35,44-46,48-51]. Although they are quite heterogeneous, all of them consistently show that IBD patients in remission who have IBS-like symptoms have a worse QoL and a greater probability of suffering from depression or anxiety than those who remain asymptomatic.

**HOW DO WE TREAT FUNCTIONAL SYMPTOMS IN IBD PATIENTS IN REMISSION?**

Evidence in IBD-IBS treatment is very poor to date. It is reasonable to apply usual IBS treatment strategies (diet modification, antispasmodics, antidepressants, probiotics, *etc.*) in the meantime.

The literature addressing this question is very scarce and of little quality, mostly based on experts´ recommendations[8,38,96,97]. It seems very reasonable to follow a step-up approach to avoid over-medication in patients who very probably are already on immunosuppressive maintenance drugs.

***Diet interventions***

Some authors recommend elaborating a diary to detect foods and beverages that provoke symptoms and eliminate them whenever feasible[97]. This is not easy as noxious effects can be accumulative (*i.e.,* symptoms may appear after eating them for several days and not immediately) and dose-dependent (*i.e.,* small amounts could be well tolerated)[96]. IBS literature is rich in food lists that have been involved in symptom triggering, and most include lactose, caffeine, fat-rich foods, deep fried foods, chewing gums, alcohol and sorbitol[98,99]. In recent years efforts are being made in order to establish a more systematic and more evidence-based approach to diet management in IBS. Diets with low quantities of fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) reduce symptoms in well-designed clinical trials[100]. This strategy could be useful in IBD-IBS patients, but remains unproven[101].

***Fiber supplementation***

Hallert *et al*[102] carried out a small, placebo-controlled trial of ispaghula husk in ulcerative colitis patients in endoscopic remission who complained of several gastrointestinal symptoms. Although not defined by the authors as IBS, the symptoms they describe were those typically present in it (pain, diarrhea, urgency, constipation, bloating, *etc.*). Ispaghula was more effective than placebo in improving those symptoms so fiber supplementation could be beneficial. In contrast, other authors recommend fiber reduction based on the fact that fiber, especially the insoluble subtype, can exacerbate symptoms in IBS (mainly bloating and flatulence)[103-105].

***Antispasmodics and antidiarrheals***

Antispasmodics as a group are useful in IBS management and have a favorable safety profile[105,106]. They could be used in quiescent IBD patients with IBS-like symptoms, although no specific trials have been published to explore their efficacy. The theoretical risk exists of inducing toxic megacolon if IBD is active[103,107].

Loperamide has no clearly proven efficacy in treating IBS but can nevertheless be useful to manage diarrhea[105,106]. It has to be used with caution if at all during a flare, as it could induce a toxic megacolon[108,109]. A placebo-controlled trial in CD patients with chronic diarrhea showed benefits of loperamide in alleviating symptoms, so its judicious use could offer satisfactory relief in patients in remission with ongoing diarrhea[103,110].

***Antidepressants***

Antidepressants as a group, both tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors (SSRI), are effective in providing global symptom relief in IBS[105,106]. Besides their neuromodulatory action they could exert an anti-inflammatory effect, as shown in animal models[111]. Most publications[112] referring to use of antidepressants in IBD are case reports that globally suggest a beneficial effect of these drugs not only in psychological symptoms but also in somatic ones. A more recent retrospective study has shown that IBD patients with concurrent depression who were under high dose antidepressant regimens had fewer disease flares and had less need of steroids[113]. Iskandar *et al*[114] have published the only original work to date that addresses specifically the potential utility of antidepressants in IBD-IBS. In their retrospective cohort study they compared the efficacy of low dose TCAs in 81 IBD patients in remission or with mild disease who complained of ongoing gastrointestinal symptoms, with that registered in a cohort of IBS patients. At least moderate improvement was achieved in 59.3% of IBD patients (higher in UC patients), similar to the proportion obtained in IBS. Data on other antidepressants such as SSRI in IBD are lacking.

***Any other options?***

No other treatments have been explored in IBD-IBS, but there are several fields very interesting for future research. Involvement of gut flora in both IBS and IBD (see above), efficacy of non-absorbable antibiotic rifaximin and of probiotics in IBS[105,106], and promising results of probiotics in UC[115] suggest that intestinal microbiome modulation could be useful in IBD-IBS treatment. Hypersensitivity and central nervous system involvement make psychological therapies, also tested in IBS[105,106], an additional interesting option to be evaluated in the future.

**CONCLUSION**

IBD patients in remission suffer quite frequently from symptoms that resemble IBS. So-called IBD-IBS is probably secondary to several factors, including post-inflammatory dysmotility and hypersensitivity, mast cell activation and increased epithelial permeability. Even though these patients are in remission their quality of life can be as low as during an acute flare, so an effort should be undertaken to recognize and treat this condition as satisfactorily as possible. Evidence on best management options of these patients is almost nonexistent. It seems reasonable to use the same drugs that have proven efficacy in IBS, such as antispasmodics and antidepressants, while we wait for future prospective trials.

Concurrence of IBS and IBD, existence of post-infectious IBS and the common pathogenic mechanisms between both entities, teach us that the classic functional-organic dichotomy is very probably obsolete. The old schema would be substituted by a unifying biopsychosocial model according to which we should not limit our therapeutic efforts to resolving inflammation but rather extend our scope to treatment of any symptoms patients report that impair their QoL and psychological well-being.

**ACKNOWLEDGEMENTS**

We would like to thank Dr. Antonio López San Román for his valuable advice and recommendations in the drafting of the manuscript.

**REFERENCES**

1 **Isgar B**, Harman M, Kaye MD, Whorwell PJ. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. *Gut* 1983; **24**: 190-192 [PMID: 6826101 DOI: 10.1136/gut.24.3.190]

2 **Simrén M**, Axelsson J, Gillberg R, Abrahamsson H, Svedlund J, Björnsson ES. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* 2002; **97**: 389-396 [PMID: 11866278 DOI: 10.1016/S0002-9270(01)04037-0]

3 **Barratt SM**, Leeds JS, Robinson K, Shah PJ, Lobo AJ, McAlindon ME, Sanders DS. Reflux and irritable bowel syndrome are negative predictors of quality of life in coeliac disease and inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2011; **23**: 159-165 [PMID: 21178777 DOI: 10.1097/MEG.0b013e328342a547]

4 **Bryant RV**, van Langenberg DR, Holtmann GJ, Andrews JM. Functional gastrointestinal disorders in inflammatory bowel disease: impact on quality of life and psychological status. *J Gastroenterol Hepatol* 2011; **26**: 916-923 [PMID: 21214889 DOI: 10.1111/j.1440-1746.2011.06624.x]

5 **Berrill JW**, Green JT, Hood K, Campbell AK. Symptoms of irritable bowel syndrome in patients with inflammatory bowel disease: examining the role of sub-clinical inflammation and the impact on clinical assessment of disease activity. *Aliment Pharmacol Ther* 2013; **38**: 44-51 [PMID: 23668698 DOI: 10.1111/apt.12335]

6 **Bercik P**, Verdu EF, Collins SM. Is irritable bowel syndrome a low-grade inflammatory bowel disease? *Gastroenterol Clin North Am* 2005; **34**: 235-245, vi-vii [PMID: 15862932 DOI: 10.1016/j.gtc.2005.02.007]

7 **Grover M**, Herfarth H, Drossman DA. The functional-organic dichotomy: postinfectious irritable bowel syndrome and inflammatory bowel disease-irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2009; **7**: 48-53 [PMID: 18848909 DOI: 10.1016/j.cgh.2008.08.032]

8 **Long MD**, Drossman DA. Inflammatory bowel disease, irritable bowel syndrome, or what?: A challenge to the functional-organic dichotomy. *Am J Gastroenterol* 2010; **105**: 1796-1798 [PMID: 20686466 DOI: 10.1038/ajg.2010.162]

9 **Sandborn WJ**, Feagan BG, Hanauer SB, Lochs H, Löfberg R, Modigliani R, Present DH, Rutgeerts P, Schölmerich J, Stange EF, Sutherland LR. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. *Gastroenterology* 2002; **122**: 512-530 [PMID: 11832465 DOI: 10.1053/gast.2002.31072]

10 **Lahiff C**, Safaie P, Awais A, Akbari M, Gashin L, Sheth S, Lembo A, Leffler D, Moss AC, Cheifetz AS. The Crohn's disease activity index (CDAI) is similarly elevated in patients with Crohn's disease and in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2013; **37**: 786-794 [PMID: 23432394 DOI: 10.1111/apt.12262]

11 **Papay P**, Ignjatovic A, Karmiris K, Amarante H, Milheller P, Feagan B, D'Haens G, Marteau P, Reinisch W, Sturm A, Steinwurz F, Egan L, Panés J, Louis E, Colombel JF, Panaccione R. Optimising monitoring in the management of Crohn's disease: a physician's perspective. *J Crohns Colitis* 2013; **7**: 653-669 [PMID: 23562672 DOI: 10.1016/j.crohns.2013.02.005]

12 **Bouguen G**, Levesque BG, Feagan BG, Kavanaugh A, Peyrin-Biroulet L, Colombel JF, Hanauer SB, Sandborn WJ. Treat to target: a proposed new paradigm for the management of Crohn's disease. *Clin Gastroenterol Hepatol* 2015; **13**: 1042-1050.e2 [PMID: 24036054 DOI: 10.1016/j.cgh.2013.09.006]

13 **Bruining DH**, Sandborn WJ. Do not assume symptoms indicate failure of anti-tumor necrosis factor therapy in Crohn's disease. *Clin Gastroenterol Hepatol* 2011; **9**: 395-399 [PMID: 21277392 DOI: 10.1016/j.cgh.2011.01.019]

14 **Chen WC**, Quigley EM. Commentary: irritable bowel syndrome and the CDAI--misleading activity by straw men. *Aliment Pharmacol Ther* 2013; **37**: 1020-1021 [PMID: 23590538 DOI: 10.1111/apt.12287]

15 **D'Incà R**, Caccaro R. Measuring disease activity in Crohn's disease: what is currently available to the clinician. *Clin Exp Gastroenterol* 2014; **7**: 151-161 [PMID: 24876789 DOI: 10.2147/CEG.S41413]

16 **Tielbeek JA**, Makanyanga JC, Bipat S, Pendsé DA, Nio CY, Vos FM, Taylor SA, Stoker J. Grading Crohn disease activity with MRI: interobserver variability of MRI features, MRI scoring of severity, and correlation with Crohn disease endoscopic index of severity. *AJR Am J Roentgenol* 2013; **201**: 1220-1228 [PMID: 24261360 DOI: 10.2214/AJR.12.10341]

17 **Kiss LS**, Szamosi T, Molnar T, Miheller P, Lakatos L, Vincze A, Palatka K, Barta Z, Gasztonyi B, Salamon A, Horvath G, Tóth GT, Farkas K, Banai J, Tulassay Z, Nagy F, Szenes M, Veres G, Lovasz BD, Vegh Z, Golovics PA, Szathmari M, Papp M, Lakatos PL. Early clinical remission and normalisation of CRP are the strongest predictors of efficacy, mucosal healing and dose escalation during the first year of adalimumab therapy in Crohn's disease. *Aliment Pharmacol Ther* 2011; **34**: 911-922 [PMID: 21883326 DOI: 10.1111/j.1365-2036.2011.04827]

18 **Jürgens M**, Mahachie John JM, Cleynen I, Schnitzler F, Fidder H, van Moerkercke W, Ballet V, Noman M, Hoffman I, van Assche G, Rutgeerts PJ, van Steen K, Vermeire S. Levels of C-reactive protein are associated with response to infliximab therapy in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2011; **9**: 421-427.e1 [PMID: 21334460 DOI: 10.1016/j.cgh.2011.02.008]

19 **Henriksen M**, Jahnsen J, Lygren I, Stray N, Sauar J, Vatn MH, Moum B. C-reactive protein: a predictive factor and marker of inflammation in inflammatory bowel disease. Results from a prospective population-based study. *Gut* 2008; **57**: 1518-1523 [PMID: 18566104 DOI: 10.1136/gut.2007]

20 **Denis MA**, Reenaers C, Fontaine F, Belaïche J, Louis E. Assessment of endoscopic activity index and biological inflammatory markers in clinically active Crohn's disease with normal C-reactive protein serum level. *Inflamm Bowel Dis* 2007; **13**: 1100-1105 [PMID: 17508418 DOI: 10.1002/ibd.20178]

21 **Däbritz J**, Musci J, Foell D. Diagnostic utility of faecal biomarkers in patients with irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 363-375 [PMID: 24574706 DOI: 10.3748/wjg.v20.i2.363]

22 **Waugh N**, Cummins E, Royle P, Kandala NB, Shyangdan D, Arasaradnam R, Clar C, Johnston R. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. *Health Technol Assess* 2013; **17**: xv-xix, 1-211 [PMID: 24286461 DOI: 10.3310/hta17550]

23 **Sipponen T**, Savilahti E, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Crohn's disease activity assessed by fecal calprotectin and lactoferrin: correlation with Crohn's disease activity index and endoscopic findings. *Inflamm Bowel Dis* 2008; **14**: 40-46 [PMID: 18022866 DOI: 10.1002/ibd.20490]

24 **Langhorst J**, Elsenbruch S, Koelzer J, Rueffer A, Michalsen A, Dobos GJ. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. *Am J Gastroenterol* 2008; **103**: 162-169 [PMID: 17916108 DOI: 10.1111/j.1572-0241.2007.01556.x]

25 **Schoepfer AM**, Beglinger C, Straumann A, Trummler M, Vavricka SR, Bruegger LE, Seibold F. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol* 2010; **105**: 162-169 [PMID: 19755969 DOI: 10.1038/ajg.2009.545]

26 **Røseth AG**, Aadland E, Jahnsen J, Raknerud N. Assessment of disease activity in ulcerative colitis by faecal calprotectin, a novel granulocyte marker protein. *Digestion* 1997; **58**: 176-180 [PMID: 9144308 DOI: 10.1159/000201441]

27 **D'Haens G**, Ferrante M, Vermeire S, Baert F, Noman M, Moortgat L, Geens P, Iwens D, Aerden I, Van Assche G, Van Olmen G, Rutgeerts P. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis* 2012; **18**: 2218-2224 [PMID: 22344983 DOI: 10.1002/ibd.22917]

28 **Mao R**, Xiao YL, Gao X, Chen BL, He Y, Yang L, Hu PJ, Chen MH. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. *Inflamm Bowel Dis* 2012; **18**: 1894-1899 [PMID: 22238138 DOI: 10.1002/ibd.22861]

29 **Sands BE**, Ooi CJ. A survey of methodological variation in the Crohn's disease activity index. *Inflamm Bowel Dis* 2005; **11**: 133-138 [PMID: 15677906 DOI: 10.1097/00054725-200502000-00006]

30 **Sipponen T**, Savilahti E, Kärkkäinen P, Kolho KL, Nuutinen H, Turunen U, Färkkilä M. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. *Inflamm Bowel Dis* 2008; **14**: 1392-1398 [PMID: 18484671 DOI: 10.1002/ibd.20490]

31 **Sipponen T**, Björkesten CG, Färkkilä M, Nuutinen H, Savilahti E, Kolho KL. Faecal calprotectin and lactoferrin are reliable surrogate markers of endoscopic response during Crohn's disease treatment. *Scand J Gastroenterol* 2010; **45**: 325-331 [PMID: 20034360 DOI: 10.3109/00365520903483650]

32 **Lin JF**, Chen JM, Zuo JH, Yu A, Xiao ZJ, Deng FH, Nie B, Jiang B. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. *Inflamm Bowel Dis* 2014; **20**: 1407-1415 [PMID: 24983982 DOI: 10.1097/MIB.0000000000000057]

33 **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, 1789-1794; quiz 1795 [PMID: 20389294 DOI: 10.1038/ajg.2010.156]

34 **Jelsness-Jørgensen LP**, Bernklev T, Moum B. Calprotectin Is a Useful Tool in Distinguishing Coexisting Irritable Bowel-Like Symptoms from That of Occult Inflammation among Inflammatory Bowel Disease Patients in Remission. *Gastroenterol Res Pract* 2013; **2013**: 620707 [PMID: 23476638 DOI: 10.1155/2013/620707]

35 **Jonefjäll B**, Strid H, Ohman L, Svedlund J, Bergstedt A, Simren M. Characterization of IBS-like symptoms in patients with ulcerative colitis in clinical remission. *Neurogastroenterol Motil* 2013; **25**: 756-e578 [PMID: 23731196 DOI: 10.1111/nmo.12163]

36 **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**: 1107-1112 [PMID: 14653830 DOI: 10.1046/j.1365-2036.2003.01800.x]

37 **Lenicek M**, Duricova D, Komarek V, Gabrysova B, Lukas M, Smerhovsky Z, Vitek L. Bile acid malabsorption in inflammatory bowel disease: assessment by serum markers. *Inflamm Bowel Dis* 2011; **17**: 1322-1327 [PMID: 21058331 DOI: 10.1002/ibd.21502]

38 **Camilleri M**. Managing symptoms of irritable bowel syndrome in patients with inflammatory bowel disease. *Gut* 2011; **60**: 425-428 [PMID: 21292684 DOI: 10.1136/gut.2010.234583]

39 **Thompson WG**, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Müller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; **45** Suppl 2: II43-II47 [PMID: 10457044 DOI: 10.1136/gut.45.2008.ii43]

40 **Longstreth GF**, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480-1491 [PMID: 16678561 DOI: 10.1053/j.gastro.2005.11.061]

41 **Mearin F**. [Irritable bowel syndrome: new Rome III criteria]. *Med Clin* (Barc) 2007; **128**: 335-343 [PMID: 17376361 DOI: 10.1157/13099805]

42 **Barratt HS**, Kalantzis C, Polymeros D, Forbes A. Functional symptoms in inflammatory bowel disease and their potential influence in misclassification of clinical status. *Aliment Pharmacol Ther* 2005; **21**: 141-147 [PMID: 15679763 DOI: 10.1111/j.1365-2036.2005.02314.x]

43 **Zaman MS,** Robson KM, Lembo AJ. Overlap of irritable bowel syndrome (IBS) symptoms in patients with inflammatory bowel disease (IBD). *Am J Gastroenterol* 2002; **97** Suppl: S284 [DOI: 10.1016/S0002-9270(02)05348-0]

44 **Minderhoud IM**, Oldenburg B, Wismeijer JA, van Berge Henegouwen GP, Smout AJ. IBS-like symptoms in patients with inflammatory bowel disease in remission; relationships with quality of life and coping behavior. *Dig Dis Sci* 2004; **49**: 469-474 [PMID: 15139501 DOI: 10.1023/B: DDAS.0000020506.84248.f9]

45 **Farrokhyar F**, Marshall JK, Easterbrook B, Irvine EJ. Functional gastrointestinal disorders and mood disorders in patients with inactive inflammatory bowel disease: prevalence and impact on health. *Inflamm Bowel Dis* 2006; **12**: 38-46 [PMID: 16374257 DOI: 10.1097/01.MIB.0000195391.49762.89]

46 **Ansari R**, Attari F, Razjouyan H, Etemadi A, Amjadi H, Merat S, Malekzadeh R. Ulcerative colitis and irritable bowel syndrome: relationships with quality of life. *Eur J Gastroenterol Hepatol* 2008; **20**: 46-50 [PMID: 18090990 DOI: 10.1097/MEG.0b013e3282f16a62]

47 **Mikocka-Walus AA**, Turnbull DA, Andrews JM, Moulding NT, Holtmann GJ. The effect of functional gastrointestinal disorders on psychological comorbidity and quality of life in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2008; **28**: 475-483 [PMID: 18532989 DOI: 10.1111/j.1365-2036.2008.03754.x]

48 **Piche T**, Ducrotté P, Sabate JM, Coffin B, Zerbib F, Dapoigny M, Hua M, Marine-Barjoan E, Dainese R, Hébuterne X. Impact of functional bowel symptoms on quality of life and fatigue in quiescent Crohn disease and irritable bowel syndrome. *Neurogastroenterol Motil* 2010; **22**: 626-e174 [PMID: 20403099 DOI: 10.1111/j.1365-2982.2010.01502.x]

49 **Jelsness-Jørgensen LP**, Bernklev T, Moum B. Fatigue and disease-related worries among inflammatory bowel disease patients in remission; is it a reflection of coexisting IBS-like symptoms? A short report. *J Psychosom Res* 2012; **73**: 469-472 [PMID: 23148817 DOI: 10.1016/j.jpsychores.2012.08.009]

50 **Kim ES**, Cho KB, Park KS, Jang BI, Kim KO, Jeon SW, Jung MK, Kim EY, Yang CH. Predictive factors of impaired quality of life in Korean patients with inactive inflammatory bowel disease: association with functional gastrointestinal disorders and mood disorders. *J Clin Gastroenterol* 2013; **47**: e38-e44 [PMID: 23090047 DOI: 10.1097/MCG.0b013e318266fff5]

51 **Vivinus-Nébot M**, Frin-Mathy G, Bzioueche H, Dainese R, Bernard G, Anty R, Filippi J, Saint-Paul MC, Tulic MK, Verhasselt V, Hébuterne X, Piche T. Functional bowel symptoms in quiescent inflammatory bowel diseases: role of epithelial barrier disruption and low-grade inflammation. *Gut* 2014; **63**: 744-752 [PMID: 23878165 DOI: 10.1136/gutjnl-2012-304066]

52 **Fukuba N**, Ishihara S, Tada Y, Oshima N, Moriyama I, Yuki T, Kawashima K, Kushiyama Y, Fujishiro H, Kinoshita Y. Prevalence of irritable bowel syndrome-like symptoms in ulcerative colitis patients with clinical and endoscopic evidence of remission: prospective multicenter study. *Scand J Gastroenterol* 2014; **49**: 674-680 [PMID: 24646420 DOI: 10.3109/00365521.2014.898084]

53 **Manning AP**, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *Br Med J* 1978; **2**: 653-654 [PMID: 698649 DOI: 10.1136/bmj.2.6138.653]

54 **Halpin SJ**, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2012; **107**: 1474-1482 [PMID: 22929759 DOI: 10.1038/ajg.2012.260]

55 **Drossman DA**, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002; **123**: 2108-2131 [PMID: 12454866 DOI: 10.1053/gast.2002.37095]

56 **Hungin AP**, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther* 2003; **17**: 643-650 [PMID: 12641512 DOI: 10.1046/j.1365-2036.2003.01456.x]

57 **Hungin AP**, Chang L, Locke GR, Dennis EH, Barghout V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. *Aliment Pharmacol Ther* 2005; **21**: 1365-1375 [PMID: 15932367 DOI: 10.1111/j.1365-2036.2005.02463.x]

58 **Lovell RM**, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 2012; **10**: 712-721.e4 [PMID: 22426087 DOI: 10.1016/j.cgh.2012.02.029]

59 **Kristjánsson G**, Venge P, Wanders A, Lööf L, Hällgren R. Clinical and subclinical intestinal inflammation assessed by the mucosal patch technique: studies of mucosal neutrophil and eosinophil activation in inflammatory bowel diseases and irritable bowel syndrome. *Gut* 2004; **53**: 1806-1812 [PMID: 15542519 DOI: 10.1136/gut.2003.036418]

60 **Ahn JY**, Lee KH, Choi CH, Kim JW, Lee HW, Kim JW, Kim MK, Kwon GY, Han S, Kim SE, Kim SM, Chang SK. Colonic mucosal immune activity in irritable bowel syndrome: comparison with healthy controls and patients with ulcerative colitis. *Dig Dis Sci* 2014; **59**: 1001-1011 [PMID: 24282051 DOI: 10.1007/s10620-013-2930-4]

61 **Keszthelyi D**, Jonkers DM, Hamer HM, Masclee AA. Letter: the role of sub-clinical inflammation and TRPV1 in the development of IBS-like symptoms in ulcerative colitis in remission. *Aliment Pharmacol Ther* 2013; **38**: 560-561 [PMID: 23937469 DOI: 10.1111/apt.12409]

62 **Annese V**, Bassotti G, Napolitano G, Usai P, Andriulli A, Vantrappen G. Gastrointestinal motility disorders in patients with inactive Crohn's disease. *Scand J Gastroenterol* 1997; **32**: 1107-1117 [PMID: 9399391 DOI: 10.3109/00365529709002989]

63 **Bassotti G**, de Roberto G, Chistolini F, Sietchiping-Nzepa F, Morelli O, Morelli A. Twenty-four-hour manometric study of colonic propulsive activity in patients with diarrhea due to inflammatory (ulcerative colitis) and non-inflammatory (irritable bowel syndrome) conditions. *Int J Colorectal Dis* 2004; **19**: 493-497 [PMID: 15083326 DOI: 10.1007/s00384-004-0604-6]

64 **Bassotti G**, Villanacci V, Mazzocchi A, Castellani D, Giuliano V, Corsi S, Morelli A. Colonic propulsive and postprandial motor activity in patients with ulcerative colitis in remission. *Eur J Gastroenterol Hepatol* 2006; **18**: 507-510 [PMID: 16607145 DOI: 10.1097/00042737-200605000-00008]

65 **Minderhoud IM**, Smout AJ, Oldenburg B, Samsom M. A pilot study on chemospecific duodenal visceral sensitivity in inflammatory bowel disease in remission. *Digestion* 2006; **73**: 151-159 [PMID: 16837799 DOI: 10.1159/000094522]

66 **Lindgren S**, Stewenius J, Sjölund K, Lilja B, Sundkvist G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. *Scand J Gastroenterol* 1993; **28**: 638-642 [PMID: 8362220 DOI: 10.3109/00365529309096103]

67 **Coruzzi P**, Castiglioni P, Parati G, Brambilla V, Brambilla L, Gualerzi M, Cademartiri F, Franzè A, De Angelis G, Di Rienzo M, Di Mario F. Autonomic cardiovascular regulation in quiescent ulcerative colitis and Crohn's disease. *Eur J Clin Invest* 2007; **37**: 964-970 [PMID: 18036030 DOI: 10.1111/j.1365-2362.2007.01887.x]

68 **Sharma P**, Makharia GK, Ahuja V, Dwivedi SN, Deepak KK. Autonomic dysfunctions in patients with inflammatory bowel disease in clinical remission. *Dig Dis Sci* 2009; **54**: 853-861 [PMID: 18712478 DOI: 10.1007/s10620-008-0424-6]

69 **Ananthakrishnan AN**, Issa M, Barboi A, Jaradeh S, Zadvornova Y, Skaros S, Johnson K, Otterson MF, Binion DG. Impact of autonomic dysfunction on inflammatory bowel disease. *J Clin Gastroenterol* 2010; **44**: 272-279 [PMID: 19727003 DOI: 10.1097/MCG.0b013e3181b2682a]

70 **Bernstein CN**, Niazi N, Robert M, Mertz H, Kodner A, Munakata J, Naliboff B, Mayer EA. Rectal afferent function in patients with inflammatory and functional intestinal disorders. *Pain* 1996; **66**: 151-161 [PMID: 8880836 DOI: 10.1016/0304-3959(96)03062-X]

71 **Chang L**, Munakata J, Mayer EA, Schmulson MJ, Johnson TD, Bernstein CN, Saba L, Naliboff B, Anton PA, Matin K. Perceptual responses in patients with inflammatory and functional bowel disease. *Gut* 2000; **47**: 497-505 [PMID: 10986209 DOI: 10.1136/gut.47.4.497]

72 **Mayer EA**, Berman S, Suyenobu B, Labus J, Mandelkern MA, Naliboff BD, Chang L. Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis. *Pain* 2005; **115**: 398-409 [PMID: 15911167 DOI: 10.1016/j.pain.2005.03.023]

73 **Faure C**, Giguère L. Functional gastrointestinal disorders and visceral hypersensitivity in children and adolescents suffering from Crohn's disease. *Inflamm Bowel Dis* 2008; **14**: 1569-1574 [PMID: 18521915 DOI: 10.1002/ibd.20506]

74 **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**: 767-774 [PMID: 20551462 DOI: 10.1136/gut.2009.194449]

75 **Keszthelyi D**, Troost FJ, Jonkers DM, Helyes Z, Hamer HM, Ludidi S, Vanhoutvin S, Venema K, Dekker J, Szolcsányi J, Masclee AA. Alterations in mucosal neuropeptides in patients with irritable bowel syndrome and ulcerative colitis in remission: a role in pain symptom generation? *Eur J Pain* 2013; **17**: 1299-1306 [PMID: 23529955 DOI: 10.1002/j.1532-2149.2013.00309.x]

76 **Akbar A**, Yiangou Y, Facer P, Walters JR, Anand P, Ghosh S. Increased capsaicin receptor TRPV1-expressing sensory fibres in irritable bowel syndrome and their correlation with abdominal pain. *Gut* 2008; **57**: 923-929 [PMID: 18252749 DOI: 10.1136/gut.2007.138982]

77 **Barbara G**, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, Grady EF, Bunnett NW, Collins SM, Corinaldesi R. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004; **126**: 693-702 [PMID: 14988823 DOI: 10.1053/j.gastro.2003.11.055]

78 **van Hoboken EA**, Thijssen AY, Verhaaren R, van der Veek PP, Prins FA, Verspaget HW, Masclee AA. Symptoms in patients with ulcerative colitis in remission are associated with visceral hypersensitivity and mast cell activity. *Scand J Gastroenterol* 2011; **46**: 981-987 [PMID: 21623672 DOI: 10.3109/00365521.2011.579156]

79 **Minderhoud IM**, Oldenburg B, Schipper ME, ter Linde JJ, Samsom M. Serotonin synthesis and uptake in symptomatic patients with Crohn's disease in remission. *Clin Gastroenterol Hepatol* 2007; **5**: 714-720 [PMID: 17481962 DOI: 10.1016/j.cgh.2007.02.013]

80 **Piche T**, Barbara G, Aubert P, Bruley des Varannes S, Dainese R, Nano JL, Cremon C, Stanghellini V, De Giorgio R, Galmiche JP, Neunlist M. Impaired intestinal barrier integrity in the colon of patients with irritable bowel syndrome: involvement of soluble mediators. *Gut* 2009; **58**: 196-201 [PMID: 18824556 DOI: 10.1136/gut.2007.140806]

81 **Gecse K**, Róka R, Séra T, Rosztóczy A, Annaházi A, Izbéki F, Nagy F, Molnár T, Szepes Z, Pávics L, Bueno L, Wittmann T. Leaky gut in patients with diarrhea-predominant irritable bowel syndrome and inactive ulcerative colitis. *Digestion* 2012; **85**: 40-46 [PMID: 22179430 DOI: 10.1159/000333083]

82 **D'Incà R**, Di Leo V, Corrao G, Martines D, D'Odorico A, Mestriner C, Venturi C, Longo G, Sturniolo GC. Intestinal permeability test as a predictor of clinical course in Crohn's disease. *Am J Gastroenterol* 1999; **94**: 2956-2960 [PMID: 10520851 DOI: 10.1111/j.1572-0241.1999.01444.x]

83 **Arnott ID**, Kingstone K, Ghosh S. Abnormal intestinal permeability predicts relapse in inactive Crohn disease. *Scand J Gastroenterol* 2000; **35**: 1163-1169 [PMID: 11145287 DOI: 10.1080/003655200750056637]

84 **Salonen A**, de Vos WM, Palva A. Gastrointestinal microbiota in irritable bowel syndrome: present state and perspectives. *Microbiology* 2010; **156**: 3205-3215 [PMID: 20705664 DOI: 10.1099/mic.0.043257-0]

85 **Carroll IM**, Ringel-Kulka T, Siddle JP, Ringel Y. Alterations in composition and diversity of the intestinal microbiota in patients with diarrhea-predominant irritable bowel syndrome. *Neurogastroenterol Motil* 2012; **24**: 521-530, e248 [PMID: 22339879 DOI: 10.1111/j.1365-2982.2012.01891.x]

86 **Nagalingam NA**, Lynch SV. Role of the microbiota in inflammatory bowel diseases. *Inflamm Bowel Dis* 2012; **18**: 968-984 [PMID: 21936031 DOI: 10.1002/ibd.21866]

87 **Halvorson HA**, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome--a meta-analysis. *Am J Gastroenterol* 2006; **101**: 1894-1899; quiz 1942 [PMID: 16928253 DOI: 10.1111/j.1572-0241.2006.00654.x]

88 **Thabane M**, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther* 2007; **26**: 535-544 [PMID: 17661757 DOI: 10.1111/j.1365-2036.2007.03399.x]

89 **Gwee KA**, Leong YL, Graham C, McKendrick MW, Collins SM, Walters SJ, Underwood JE, Read NW. The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999; **44**: 400-406 [PMID: 10026328 DOI: 10.1136/gut.44.3.400]

90 **Gwee KA**. Post-Infectious Irritable Bowel Syndrome, an Inflammation-Immunological Model with Relevance for Other IBS and Functional Dyspepsia. *J Neurogastroenterol Motil* 2010; **16**: 30-34 [PMID: 20535323 DOI: 10.5056/jnm.2010.16.1.30]

91 **Qin HY**, Cheng CW, Tang XD, Bian ZX. Impact of psychological stress on irritable bowel syndrome. *World J Gastroenterol* 2014; **20**: 14126-14131 [PMID: 25339801 DOI: 10.3748/wjg.v20.i39.14126]

92 **Triantafillidis JK**, Merikas E, Gikas A. Psychological factors and stress in inflammatory bowel disease. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 225-238 [PMID: 23445232 DOI: 10.1586/egh.13.4]

93 **Mitchell A**, Guyatt G, Singer J, Irvine EJ, Goodacre R, Tompkins C, Williams N, Wagner F. Quality of life in patients with inflammatory bowel disease. *J Clin Gastroenterol* 1988; **10**: 306-310 [PMID: 2980766 DOI: 10.1097/00004836-198806000-00014]

94 **Irvine EJ**, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D, Saibil F, McDonald JW. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology* 1994; **106**: 287-296 [PMID: 8299896]

95 **Hjortswang H**, Ström M, Almer S. Health-related quality of life in Swedish patients with ulcerative colitis. *Am J Gastroenterol* 1998; **93**: 2203-2211 [PMID: 9820397 DOI: 10.1111/j.1572-0241.1998.00537.x]

96 **Ginsburg PM**, Bayless TM. Managing Functional Disturbances in Patients with Inflammatory Bowel Disease. *Curr Treat Options Gastroenterol* 2005; **8**: 211-221 [PMID: 15913510 DOI: 10.1007/s11938-005-0013-0]

97 **MacDermott RP**. Treatment of irritable bowel syndrome in outpatients with inflammatory bowel disease using a food and beverage intolerance, food and beverage avoidance diet. *Inflamm Bowel Dis* 2007; **13**: 91-96 [PMID: 17206644 DOI: 10.1002/ibd.20048]

98 **Dapoigny M**, Stockbrügger RW, Azpiroz F, Collins S, Coremans G, Müller-Lissner S, Oberndorff A, Pace F, Smout A, Vatn M, Whorwell P. Role of alimentation in irritable bowel syndrome. *Digestion* 2003; **67**: 225-233 [PMID: 12966230 DOI: 10.1159/000072061]

99 **Lea R**, Whorwell PJ. The role of food intolerance in irritable bowel syndrome. *Gastroenterol Clin North Am* 2005; **34**: 247-255 [PMID: 15862933 DOI: 10.1016/j.gtc.2005.02.005]

100 **Halmos EP**, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology* 2014; **146**: 67-75.e5 [PMID: 24076059 DOI: 10.1053/j.gastro.2013.09.046]

101 **Schwender B**, Floch MH. Should FODMAP withdrawal be tried in inflammatory bowel disease patients with irritable bowel syndrome? *J Clin Gastroenterol* 2014; **48**: 393-394 [PMID: 24705090 DOI: 10.1097/MCG.0000000000000127]

102 **Hallert C**, Kaldma M, Petersson BG. Ispaghula husk may relieve gastrointestinal symptoms in ulcerative colitis in remission. *Scand J Gastroenterol* 1991; **26**: 747-750 [PMID: 1654592 DOI: 10.3109/00365529108998594]

103 **Meng J**, Agrawal A, Whorwell PJ. Refractory inflammatory bowel disease-could it be an irritable bowel? *Nat Rev Gastroenterol Hepatol* 2013; **10**: 58-61 [PMID: 22965430 DOI: 10.1038/nrgastro.2012.173]

104 **Bijkerk CJ**, Muris JW, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004; **19**: 245-251 [PMID: 14984370 DOI: 10.1111/j.0269-2813.2004.01862.x]

105 **Moayyedi P**, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Ford AC. The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gastroenterol* 2014; **109**: 1367-1374 [PMID: 25070054 DOI: 10.1038/ajg.2014.187]

106 **Weinberg DS**, Smalley W, Heidelbaugh JJ, Sultan S. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. *Gastroenterology* 2014; **147**: 1146-1148 [PMID: 25224526 DOI: 10.1053/j.gastro.2014.09.001]

107 **Pezzone MA**, Wald A. Functional bowel disorders in inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; **31**: 347-357 [PMID: 12122742 DOI: 10.1016/S0889-8553(01)00021-8]

108 **Whorwell PJ**, Isaacson P. Toxic dilatation of colon in Crohn's disease. *Lancet* 1981; **2**: 1334-1337 [PMID: 6118726 DOI: 10.1016/S0140-6736(81)91350-7]

109 **Cuadrado-Gómez LM**, Arranz-Caso A, Albarrán-Hernández F, Alvarez de Mon M. [Toxic megacolon caused by loperamide as initial form of Crohn disease]. *Rev Clin Esp* 1994; **194**: 201-202 [PMID: 8008961]

110 **van Outryve M**, Toussaint J. Loperamide oxide for the treatment of chronic diarrhoea in Crohn's disease. *J Int Med Res* 1995; **23**: 335-341 [PMID: 8529776]

111 **Ghia JE**, Blennerhassett P, Collins SM. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression. *J Clin Invest* 2008; **118**: 2209-2218 [PMID: 18451995 DOI: 10.1172/JCI32849]

112 **Mikocka-Walus AA**, Turnbull DA, Moulding NT, Wilson IG, Andrews JM, Holtmann GJ. Antidepressants and inflammatory bowel disease: a systematic review. *Clin Pract Epidemiol Ment Health* 2006; **2**: 24 [PMID: 16984660 DOI: 10.1186/1745-0179-2-24]

113 **Goodhand JR**, Greig FI, Koodun Y, McDermott A, Wahed M, Langmead L, Rampton DS. Do antidepressants influence the disease course in inflammatory bowel disease? A retrospective case-matched observational study. *Inflamm Bowel Dis* 2012; **18**: 1232-1239 [PMID: 22234954 DOI: 10.1002/ibd.21846]

114 **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**: 423-429 [PMID: 24406434 DOI: 10.1097/MCG.0000000000000049]

115 **Whelan K**, Quigley EM. Probiotics in the management of irritable bowel syndrome and inflammatory bowel disease. *Curr Opin Gastroenterol* 2013; **29**: 184-189 [PMID: 23286925 DOI: 10.1097/MOG.0b013e32835d7bba]

**P-Reviewer:** Gaertner W, Raman M, Sipahi AM **S-Editor:** Tian YL

**L-Editor: E-Editor:**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 1 Summary of studies that have determined prevalence of IBS-like symptoms in quiescent IBD** | | | | | | |
| **Ref.** | **Type** | **Sample size (CD/UC)** | **Criteria used to define IBD remission** | **Exclusions (IBD characteristics or previous surgery)** | **Criteria used to define IBS** | **IBD-IBS prevalence *n* (%)** |
| Isgar *et al*[1] | Case-control | 98 (0/98)  98 non-IBD controls | Endoscopic remission, steroid-free | Not further specified | Manning | UC: 33 (33.7) |
| Simren  *et al*[2] | Cross-sectional | 83 (40/43) | CD: Physician global assessment, endoscopic/radiological remission and normal inflammatory markers (Hb, ESR, CRP, platelets, albumin).  UC: Endoscopic remission, no blood nor mucus, normal CRP. | Stenotic CD.  CD patients with > 2 surgeries.  Significant comorbidities. | Gastrointestinal symptom questionnaire validated | 37 (44.6)  CD: 23 (57)  UC: 14 (33) |
| Zaman  *et al*[43] | Cross-sectional | 55 (30/25) | Stable symptoms, no changes in medication for 3 months | Not available | Rome II | 35 (63.6)  CD: 20 (66.7)  UC: 15 (60) |
| Minderhoud *et al*[44] | Case-control | 107(34/73)  66 non-IBD controls | CD: CDAI<150  UC: CAIUC<10 | Significant comorbidities. | Manning  Rome II | Manning: 33 (30.8)  CD: 8 (23.5)  UC: 25 (34.2)  Rome II: 37 (34.6)  CD: 14 (41.7)  UC: 23 (31.5) |
| Farrokhyar  *et al*[45] | Cross-sectional | 149 (105/44) | No changes/addition of medication nor change dosage in the last year | Not further specified | Rome II | 31 (20.8)  CD: 27 (26)  UC: 4 (9.1) |
| Ansari *et al*[46] | Case-control | 50 (0/50)  100 non-IBD controls | Mayo score ≤ 2 (bleeding score = 0, endoscopic score 0-1) | Not further specified | Rome II | UC: 23 (46) |
| Keohane  *et al*[33] | Cross-sectional | 106 (62/44) | CD: CDAI < 150  UC: UCAI ≤ 3  For both: physician´s global assessment, CRP < 10 mg/L, no use of steroids or biological agents in previous 6 mo | Not further specified | Rome II | 54 (50.9)  CD: 37 (59.7)  UC: 17 (38.6) |
| Piche *et al*[48] | Cross-sectional | 92 (92/0) | CDAI < 150 for > 6 mo, endoscopic/radiologic remission (CDEIS < 6), normal inflammatory markers (CRP, Hb, ESR, platelets, albumin). | Stenosis.  CD patients with previous surgery.  Recent corticoid use. | Rome III | CD: 42 (45.7) |
| Barratt  *et al*[3] | Case-control | 276 (110/166)  348 non-IBD controls | CD: HBI < 5  UC: SCCAI < 5 | Not further specified | Rome II | 31 (11.2)  CD: 14 (12)  UC: 17 (9) |
| Bryant  *et al*[4] | Cross-sectional | 93 (47/43)1 | Physician´s global assessment using inflammatory markers, histological and endoscopic activity and clinical data. | Not further specified | Rome III | 12 (12.9)  (no CD/UC differentiation) |
| Jelsness-Jorgensen  *et al*[49] | Cross-sectional | 89 (28/61) | CD: SCDAI < 4.  UC: SCCAI < 3.  No current steroid treatment. | Not further specified | Rome II  Rome III | Rome II: 21 (23.6)  CD: 6 (21.4)  UC: 15 (24.6)  Rome III: 30 (33.7)  CD: 8 (28.6)  UC: 22 (36.1) |
| Kim *et al*[50] | Cross-sectional | 226 (107/119) | No changes on therapy in last year, normal limits of CRP, hemoglobin, no blood or mucus in stools for UC. | CD with stenotic/ penetrating phenotype.  Previous surgery. | Rome III | 82 (36.3)  CD: 50 (46.7)  UC: 32 (26.9) |
| Berrill  *et al*[5] | Cross-sectional | 97 (40/57) | CD: HBI < 5, CRP < 10 mg/L  UC: SCCAI < 3, CRP < 10 mg/L | Ileostomy, colostomy or total colectomy. | Rome III | 31 (32)  CD: 13 (32.5)  UC: 18 (31.6) |
| Jonefjäll  *et al*[35] | Pro-spective | 94 (0/94) | Mayo ≤ 2 (endoscopic < 1)  No relapse during 3 mo before inclusion | Significant comorbidities. | Rome II | UC: 25 (27) |
| Vivimus-Nèbot  *et al*[51] | Cross-sectional | 49 (31/18) | CD: CDAI < 150,CDEIS ≤ 4  UC: UCAI ≤ 3,Mayo = 0  For both: physician´s global assessment, CRP < 10mg/L, no use of steroids over the last year. | Stenotic or complicated CD.  Significant comorbidities. | Rome III | 18 (36.7)  CD: 11 (35.4)  UC: 7 (38) |
| Fukuba  *et al*[52] | Case control | 172 (0/172)  330 non-IBD controls | CAI ≤ 4, CRP < 5 mg/L. | Colectomy | Rome III | UC: 46 (26.7) |
| Total | - | 1836 (726/1107)1 | - | - | - | Total: 567 (30.9)  CD: 259 (38.1)2  UC: 296 (27.8)2 |

1In the original article the numbers given by the authors do not add up to the total of patients and they do not specify if the rest correspond to undetermined colitis; 2For the pooled prevalences in CD and UC, patients from study of Bryant et al have not been included as they do not state a differentiated IBS-IBD prevalence for CD and UC respectively. CD: Crohn’s disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; IBS: Irritable bowel disease; CRP: C reactive protein; Hb: Haemoglobin; ESR: Erythrocyte sedimentation rate; CDAI: Crohn’s disease activity index; CAIUC: Clinical activity index for ulcerative colitis; UCAI: Ulcerative colitis activity index; CDEIS: Crohn’s disease endoscopic index of severity; HBI: Harvey-Bradshaw index; SCCAI: Simple clinical colitis activity index; SCDAI: Simple Crohn’s disease activity index; CAI: Colitis activity index.

**Table 2 Adapted from Longstreth *et al*[40]**

|  |
| --- |
| **IBS Rome III criteria** |
| Recurrent abdominal pain or discomfort at least 3 d per month in the last 3 mo (with onset at least 6 months prior to diagnosis) associated with two or more of the following: |
| Relieved with defecation  Onset associated with a change in frequency of stools  Onset associated with a change in form (appearance) of stools |

**Table 3 Studies that explore quality of life and anxiety in IBD patients in remission with IBS-like symptoms**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Sample size (CD/UC)** | **questionnaires used** | **Results** |
| Simren *et al*[2] | 83 (40/43)  37 IBD-IBS (23/14) | GSRS  HADS  STAI  PGWB | Higher anxiety and depression scores in IBD-IBS (worst in CD). |
| Minderhoud *et al*[44] | 107 (34/73)  37 IBD-IBS (14/23) | IBDQ | Lower QoL scores in IBD-IBS. |
| Farrokhyar *et al*[45] | 149 (105/44)  31 IBD-IBS (27/4) | sIBDQ  EQ-5D | Occurence of any FGID taken in count (not only IBS-like).  Lower QoL scores in CD patients with FGID.  Difference not significant for UC. |
| Ansari *et al*[46] | 50 (0/50)  IBD-IBS: 23 (0/23) | SF-36 | Lower QoL scores in IBD-IBS than in asymptomatic and similar to patients in flare. |
| Keohane *et al*[33] | 106 (62/44)  54 IBD-IBS (37/17) | IBSQ  HADS | QoL scores only significantly lower in UC-IBS.  Levels of anxiety and depression only significantly higher in UC-IBS. |
| Piche *et al*[48] | 92 (92/0)  42 (42/0) | French-validated IBS severity scoring system  Likert scales  FIS  Short BDI  HADS | Higher severity, impact, depression and fatigue scores in CD-IBS.  No significant differences in anxiety level. |
| Barratt *et al*[3] | 276 (110/166)  31 (14/17) | SF-36  HADS | No differentiation between IBD patients in remission or in active phase.  Lower QoL scores and higher anxiety, depression scores in IBD-IBS. |
| Bryant *et al*[4] | 93 (47/43)  12 (no CD/UC differentiation) | sIBDQ  HADS  BDQ-6 | Occurrence of any FGID taken in count (not only IBS-like).  Lower QoL scores and higher anxiety and depression scores in IBD patients with any FGID.  Lowest scores in IBS-like symptoms. |
| Jelsness-Jorgensen *et al*[49] | 89(28/61)  30 IBD-IBS (8/22) | FQ  RFIPC | More fatigue scores in IBD-IBS (worst in UC).  More concerns in UC-IBD (difference non significant for CD). |
| Kim *et al*[50] | 226 (107/119)  82 IBD-IBS (50/32) | EQ-5D  HADS | Occurrence of any FGID taken in count (not only IBS-like).  Lower QoL scores and higher anxiety and depression scores in UC-IBS (difference non-significant for CD). |
| Berrill *et al*[5] | 97 (40/57)  31 IBD-IBS (13/18) | HADS | No differentiation between IBD patients in remission or in active phase.  Higher anxiety and depression scores in IBD-IBS. |
| Jonefjal *et al*[35] | 94 (0/94)  IBD-IBS 25 (0/25) | HADS  SF-36 | Lower QoL scores and higher anxiety scores in UC-IBS (difference in depression score non-significant). |
| Vivinus-Nebot *et al*[51] | 49 (31/18)  18 IBD-IBS (11/7) | French-validated IBS severity scoring system | Higher severity and impact scores in IBD-IBS. |

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn’s disease; GSRS: Gastrointestinal symptom rating scale; HADS: Hospital anxiety and depression scale; STAI: Spielberger state trait anxiety inventory; PGWB: Psychological general well-being index; IBSQ: Inflammatory bowel disease questionnaire; QoL: Quality of life; sIBDQ: Inflammatory bowel disease questionnaire; EQ-5D: EuroQOL-5D; FGID: Functional gastrointestinal disorders; FIS: Fatigue impact scale; BDI: Becks depression inventory; BDQ-6: Bowel disease questionnaire-6; FQ: Fatigue questionnaire; RFIPC: Rating form of inflammatory bowel disease patients concerns.