Activitas Nervosa Superior Rediviva Volume 62 No.3-4 2020

ORIGINAL ARTICLE

Outcome of antidepressant therapy in affective disorders comorbidity in infiammatory bowel diseases (IBD): Clinical results and psychometric variables after one year of treatment

Riccardo L. Zanello [1], Cecilia Bertarelli [1], Benedetta Grancini [1], Monica F. Bosi [2], Nicolaja Girone [2], Giovanni Maconi[3], Roberto Truzoli [4,2], Bernardo M. Dell'Osso [4,2,5,6], Caterina A. Viganò [4,2]

[1] Graduate in Psychiatry, Università degli Studi di Milano, Milan, Italy. [2] Psychiatry Unit 2, H. Sacco, ASST Fatebenefratelli Sacco, Milan, Italy. [3] Gastroenterology Unit Biomedical and Clinical Sciences Dept. L. Sacco, Università degli Studi di Milano, Milan, Italy, H. Sacco, ASST Fatebenefratelli Sacco, Milan, Italy. [4] Biomedical and Clinical Sciences Dept. L. Sacco, Università degli Studi di Milano, Milan, Italy. [5] Bipolar Disorders Clinic, Dept. of Psychiatry and Behavioral Sciences, Stanford University, Stanford, USA. [6] 6CRC "Aldo Ravelli" for Neuro-technologies & Experimental Neurological Therapies, Università di Milano, Milan, Italy.

Correspondence to: Dr. Caterina Viganò, Psychiatry 2, Pad 60, Luigi Sacco Hospital, via G.B.Grassi 74, 20157, Milan, Italy
tel: +390239042980; fax: +390239043149; e-mail: caterina.vigano@unimi.it

Submitted: 2020-09-03 Accepted: 2020-10-30 Published online: 2020-11-20

Key words: **psychopathology; ulcerative colitis (uc); antidepressive agents (ad); crohn disease (cd); inflammatory bowel diseases (ibd); depressive disorders; depression; anxiety disorders**

Act Nerv Super Rediviva 2020; **62**(3-4): 95–105 ANSR62320A02

Abstract

OBJECTIVES: Assessing the effect of antidepressant therapy (AD) on the abdominal symptomatology in Inflammatory Bowel Disease (IBD) patients with mood or anxiety disorders.
METHODS: 58 IBD patients in clinical remission and without known psychiatric disorder but with positive scores in the Hospital Anxiety Depression Scale (HADS) were evaluated for the presence of anxiety and mood disorders (DSM-5 criteria) and administered the Self-report Symptoms Inventory, Revised (SCL-90-R), the Brief Coping Orientation to Problems Experienced (Brief-COPE), the Short Form-36 Health Survey (SF-36), the Hamilton Rating Scale for Anxiety (HAM-A) and Depression (HAM-D). Rectal bleeding and abdominal pain severity and evacuation frequency were evaluated. Patients with affective disorders underwent AD therapy. We analyzed and compared clinical and psychometric findings at baseline, before therapy, and at 3–6–9–12 months follow-up.
RESULTS: Of 58 patients enrolled 56,9% were diagnosed with anxiety or mood disorders. Compared to patients without psychiatric comorbidity, IBD-affective patients presented higher HAM-D and HAM-A scores, lower scores in "vitality" (SF-36), and "general anxiety" (SCL-90r) domains, poorer "positive restructuring" and "use of instrumental support" coping strategies, and increased evacuations. In the treated sample, AD therapy significantly reduced anxiety and depressive domains (HAM-A, HAM-D scores) and the data suggest a reduction of evacuation frequency.
CONCLUSION: Comorbid IBD-affective patients show decreased levels of self-perceived health and of several coping mechanisms; Although they are in clinical remission most of them present increased number of bowel movements at the baseline, which decreased during AD therapy.

Introduction

Chronic Inflammatory Bowel Diseases (IBD), represented by Crohn's Disease (CD) and Ulcerative Colitis (UC), are characterized by the presence of inflammation in the gastrointestinal tract with alternating phases of acute flares and symptomatic remission. Inflammation in CD can involve the entire gastrointestinal tract (Abraham & Cho 2009), while in UC it is localized at the colic and rectal level only. In patients suffering from IBD also coexist with frequent systemic and extra-intestinal complications. Both the diseases present an unpredictable evolution, and patients might need to undergo surgery (Ishak *et al.* 2017, Monsén *et al.* 1990). The pathogenesis of IBD is multifactorial. In genetically predisposed subjects and in the presence of dysbiosis of the gut microbiota (Jostins 2012) environmental factors can bring about an abnormal intestinal immune response. The chronic nature of IBD and its frequent onset in early adulthood (Byrne *et al.* 2017; Viganò *et al.* 2016a) cause severe stress and can lead to a reduced quality of life (Graff *et al.* 2006; Moradkhani *et al.* 2013; Ishak *et al.* 2017). Other factors are also linked to a low quality of life: repeated flares, low levels of social support, high levels of stress, and the presence of psychiatric comorbidities (Byrne *et al.* 2017; Bhamre *et al.* 2018).

The risk of mental disorders is indeed higher than in the general population (Graff *et al.* 2006; Scott *et al.* 2007; Bernstein *et al.* 2019). Several studies highlighted the comorbidity between IBD and anxiety disorders and depression (Mikocka-Walus *et al.* 2016). The prevalence of affective disorders is estimated to be around 30% in patients in clinical remission, reaching up to 60–80% during the active phase of the disease (Graff *et al.* 2009; Walker *et al.* 2008). The presence of anxious or depressive symptoms is associated with a reduction in compliance to treatments (Scott *et al.* 2007; Severs *et al.* 2017), an increase in disability (Chan *et al.* 2017) and mortality (Katon 2011). Several studies have focused on the identification of the risk factors for the development of anxiety and depression in patients suffering from IBD. Among the most analyzed factors there are socio-demographic characteristics, the activity and severity ofintestinal pathology, types of treatment and psychosocial factors (Nahon *et al.* 2012).

Considering psychosocial factors, the psychological stress deriving from the awareness of the disease, which typically presents a chronic and unpredictable course, and from the often-demanding therapies, can increase the risk of developing anxiety or depression (Choi *et al.* 2019). The risk appears to increase in the presence of negative coping strategies (McCombie *et al.* 2013; Viganò *et al.* 2016b).

An association between high levels of neurosis, impulsivity and alexithymia and a reduction in mental and physical health in patients with IBD has also been found (Fuller-Thomson *et al.* 2015). The prevalence of alexithymia in these patients is around 35% (Hopkins & Moulton 2016; Viganò *et al.* 2018). A closed correlation between this psychopathological construct and the clinical severity of functional gastrointestinal disorders is recognized (Porcelli *et al.* 1995). High levels of alexithymia lead to a greater tendency to communicate their distress through somatic symptoms rather than through verbal forms, favoring a more severe psychopathological picture and a negative overall outcome (La Barbera *et al.* 2017; Viganò *et al.* 2018).

The presence of depressive symptomatology has been shown to increase the risk of failure of biological therapy with infliximab, inhibitor of TNF-α, in the MC in active phase, suggesting the presence of a possible dynamic interference between the two pathological conditions (Persoons *et al.* 2005). There is still an open debate on the possibility that anxiety-depressive symptoms could play a role in the reactivation of the disease (Mikocka-Walus *et al.* 2016; Porcelli *et al.* 1996), as patients with high rates of depression seem also to have a higher risk of rekindling (Mardini *et al.* 2004; Mittermaier *et al.* 2004; Maconi *et al.* 2014).

Recently, some studies have investigated the effect of antidepressant (AD) therapy in IBD, finding a protective effect of AD therapy against the development of IBD when administered in anxious-depressive patients prior to a diagnosis of IBD (Frolkis *et al.* 2018). In the IBD patients presenting an affective disorder, AD therapy has also been found to be effective in reducing both the anxious-depressive and intestinal symptomatology in the short-term (Daghaghzadeh *et al.* 2015; Iskandar *et al.* 2014; Yanartas *et al.* 2016). In the long-term, the use of AD therapy seems to be associated with fewer relapses, hospitalizations and reduced the use of corticosteroids (Mikocka-Walus *et al.* 2007; Goodhand *et al.* 2012). On the other hand, recent evidence indicates that the control of disease activity in IBD may have an effect in mitigating the comorbid psychiatric symptomatology (Uguz *et al.* 2009). AD therapy exerts its effect both directly on the CNS but also on peripheral nociception, visceral sensitivity, intestinal motility (Ford *et al.* 2019), and has immunoregulatory effects (Maes 2001) and it has been shown to be effective in reducing the somatic symptoms in other gastrointestinal diseases such as IBS and dyspepsia. Up to now, all the studies available on the effect of AD in these patients have been for periods shorter than one year.

The aim of this study was to evaluate the clinical and psychometric factors associated with IBD-affective comorbidity, and the effect of one year of antidepressant therapy on IBD symptoms in patients affected by anxiety or mood disorder.

Materials and methods

Participants

In this study, we selected the participants from a cohort of 170 IBD outpatients in regular follow-up at the IBD Centre of the Gastroenterology Department and IBD

Unit of the ASST-Fatebenefratelli-Sacco University Hospital in Milan, Italy, and who were tested with the Hospital Anxiety Depression Scale - HADS administered by the attending gastroenterologists and surgeons. Those who scored positively were considered eligible for the study and underwent further psychiatric evaluation in the Outpatient Psychiatric Unit for Mood Disorders of the same hospital. The recruitment took place between January 2016 and May 2019.

All patients gave their written informed consent to participate in the study and the study was approved by the local Ethical Committee.

All patients met the inclusion and exclusion criteria below.

The study included adults patients in clinical remission namely with Crohn's Disease Activity Index (CDAI)<150 or Harvey Bradshow Index (HBI) ≤ 4 for Crohn's disease and Mayo partial score ≤2 for ulcerative colitis (UC); whether or not under maintenance tratment with 5-ASA, immunosuppressants or biologic therapies. Positive score in the HADS screening scale for anxiety-depressive symptoms (score ≥ 8).

We escluded patients with active CD or CU or patients in remission but under systemic corticosteroids treatment; patients with neurodevelopmental disorders (IQ <70); cognitive impairment; state of pregnancy; Substance Use and Alcohol Use Disorder known; presence of serious medical comorbidities not linked to IBD: neurocognitive disorder, documented head trauma, concomitant neurological pathology.

Procedure

This retrospective cohort study included a consecutive series of IBD outpatients in clinical remission, who resulted positive at the HADS evaluation. All patients underwent a gastroenterological assessment of clinical history of IBD and current signs and symptoms, aimed to confirm the clinical remission and grade the severity of symptoms. Then they were assessed through a clinical psychiatric interview by a trained psychiatrist and screened considering socio-demographic and psychiatric variables.

All IBD patients in stable (>6 months) clinical remission and confirmed psychiatric comorbidity (Major or Persistent Depressive Disorder or with Anxiety Disorder according to the DSM-5 diagnostic criteria) were prescribed a treatment with AD (SSRI's and SNRI's according to clinical criteria) and underwent a scheduled gastroenterological and psychiatric follow up with visits at 1 – 3 – 6 – 12 months. Gastroenterological evaluation assessed the main symptoms that impact on the quality of life, such as the number of bowel movements (regular as usual or increased), abdominal pain (absent/present), rectal bleeding (absent/present).

Materials

Assessment of socio-demographic and psychiatric variables was done through clinical interview: gender, age, marital status, education, employment, IBD, familiarity for IBD, age at onset of IBD, age at diagnosis of IBD, localization of intestinal disease, previous surgery, current IBD therapy, evacuation rate, abdominal pain, rectal bleeding, previous psychiatric diagnosis, current psychopharmacological therapy, previous or current day-hospital care for depression or anxiety.

Psychiatric symptomatology through the Symptom Checklist-90-R (SCL-90-R; Derogatis *et al.* 1973). The SCL-90-R is a self-report psychometric questionnaire published by the Clinical Assessment division of the Pearson Assessment & Information group and designed to evaluate a broad range of psychological problems and symptoms of psychopathology, taking into account both internalizing (depression, somatization, anxiety) and externalizing (aggression, hostility, impulsivity) symptoms. It is also used in measuring the progress and outcome of psychiatric and psychological treatments or for research purposes. It is composed of 90 items each belonging to 10 different psychopathological dimensions. The patients can select between a value ranging from 0 (absence of symptom) to 4 (severe presence of symptomatology). Raw scores for dimensional subscales are calculated by dividing the sum of scores for a dimension by the number of items in the dimension. Higher scores for a specific dimension indicate increasingly severe symptoms for that psychopathological dimension. To evaluate the presence of abnormal psychopathological symptoms, these scores are then converted to standard T-scores using the norm group appropriate for the patient to match T-store with population percentiles. Four formal norms are available (Psychiatric outpatients; Community non-patients; Psychiatric inpatients; Adolescent non-patients). Separate norms exist for both males and females. The Global Severity Index (GSI) represents a global indicator of the intensity of level or depth of discomfort complained by the subject. The internal consistency coefficient rating ranged from 0.90 for the subscales of Depression and 0.77 for Psychoticism.

Coping strategies using the Brief Coping Orientation to Problems Experienced (Brief-COPE; Carver 1997). The purpose of this scale is to identify the nature of the coping strategies implemented by patients. The brief-COPE questionnaire is self-administered and represents a multidimensional measure that evaluates the different dimensions of coping: it includes 28 questions. The patient is asked how often he's adopted a specific coping behavior before a stressful situation, rating the frequency from 1 "I haven't been doing this at all", to 4, "I've been doing this a lot". The global score for each coping strategy is obtained through the sum of the scores of the single items belonging to that strategy subscale. Higher scores indicate a more frequent use of the strategy. This psychometric test has already been used to evaluate adaptation strategies in the IBD population in a previous 2016 work (Farrell & Savage 2012) The coping strategies investigated with this scale are:

positive restructuring, diverting attention, expression, use of instrumental support, dealing operationally, denial, religion, humor, behavioral disengagement, use of emotional support, substance use, acceptance, planning, self-accusation (Baumstarck *et al.* 2017; Brasileiro *et al.* 2016). The internal consistency coefficient rating ranged from 0.90 for the subscales of Substance Use and 0.50 for Venting.

Health status perception using Short Form-36 Health Survey (SF-36; Ware & Sherbourne 1992). The questionnaire is short, self-administered and has 36 items measuring 8 variables: physical activity (10 questions), physical role (4 questions), physical pain (2 questions), general health (5 questions), vitality (4 questions), social activities (2 questions), role emotional role (3 questions) and mental health (5 questions). For each of them, the patient is asked to self-evaluate how much his current health status is interfering with it. For each variable the results are coded, summarized and transformed into a scale ranging from 0 – the worst possible greeting – to 100 – the best possible (Jenkinson *et al.* 1993). Therefore, SF-36 provides information on the physical, functional, emotional and social state of patients and helps to distinguish those with affective disorders that should be investigated (Oswald *et al.* 2008). The SF-36 was found to have had adequate internal consistency satisfying the recommended threshold value of 0.7 (Zhang *et al.* 2012).

Severity level of depressive and anxious symptoms through the Hamilton Rating Scale for Anxiety – HAM-A (Hamilton 1959) and for Depression – HAM-D (Hamilton 1960). They are very useful in monitoring symptoms over time and in evaluating response to treatment as they are more sensitive to change (Trajković *et al.* 2011). HAM-A consists of 14 elements dedicated to both psychological and somatic symptoms, which include: anxious state, tension, fear of the dark, of strangers, of the crowd, insomnia, difficulty concentrating, depressed mood, somatic symptoms such as pain, stiffness, bruxism, cardiovascular symptoms such as tachycardia, respiratory symptoms such as air hunger, gastrointestinal, genitourinary, autonomic and behavior of the subject during the examination. Each item can be assigned a numerical score from 0 – absent – to 4 – severe. A score above 17 indicates mild anxiety, above 25–30 is considered moderate-severe (Hallit *et al.* 2019; Thompson 2015). The HAM-D version we employed is composed of 21 items, each of which can be assigned a score from 0 to 4 as in the HAM-A. The scoring is based on the 17-item version and scores from 0 to 7 are considered normal, 8–16 suggest mild depression, 17–23 moderate and above 24 are indicative of severe depression (Sharp 2015). The HAM-A and HAM-D scales had adequate internal consistency satisfying the recommended threshold value of 0.70 (Maier *et al.* 1988).

Statistical analysis

We then compared the data at T0 for the subpopulations of IBD patients with and without an anxiety or mood disorder. Continuous variables were studied with the Student T test, while the categorical variables were compared using Chi-square tests. Values of $p \leq 0.05$ were considered significant.

To evaluate the trend over time of gastroenterological and psychopathological variables in patients who

Tab. 1. Socio-demographic data

		Total Sample (n=58)	With affective comorbidity (n=33)	Patients completing one year follow-up (n=15)
Age (years) average ± SD		42.9 ± 13.8	44.12 ± 14.7	48.27 ± 13.7
Gender, n (%)	Male	26 (44.6%)	13 (39.4%)	6 (40.0%)
	Females	32 (55.2%)	20 (60.6%)	9 (60.6%)
Marital status, n (%)	Single	34 (58.6%)	15 (45.5%)	5 (33.3%)
	Married	19 (32.8%)	13 (39.4%)	7 (46.7%)
	Divorced	5 (8.6%)	5 (15.2%)	3 (20.0%)
Level of Education, n (%)	Elementary school	1 (1.7%)	1 (3.0%)	0 (0%)
	Middle school	14 (24.1%)	10 (30.3%)	7 (46.7%)
	High school	32 (55.2%)	20 (60.6%)	7 (46.7%)
	University degree	11 (19.0%)	2 (6.1%)	1 (6.7%)
Employment status, n (%)	Student	7 (12.1%)	3 (9.1%)	1 (6.7%)
	Employee	34 (58.6%)	20 (60.6%)	8 (53.3%)
	Self-employed	6 (10.3%)	3 (9.1%)	2 (13.3%)
	Unemployed	7 (12.1%)	4 (12.2%)	3 (20.0%)
	Retired	4 (6.9%)	3 (9.1%)	1 (6.7%)

Tab. 2. Clinical data

			Total Sample (n=58)	With affective comorbidity (n=33)	Sample with one year follow-up (n=15)
IBD type, n (%)	Ulcerative Colitis		34 (58.6%)	17 (51.5%)	6 (40.0%)
	Crohn's Disease		24 (41.1%)	16 (48.5%)	9 (60.0%)
Familiarity for IBD, n (%)	No		47 (81.0%)	26 (78.8%)	10 (66.7%)
	Yes		11 (19.0%)	7 (21.2%)	5 (33.3%)
Age at onset of IBD symptoms (age) mean ± SD			28.6 ± 11.6	28.3 ± 13.1	27.4 ± 13.7
Age at IBD diagnosis (age) mean ± SD			30.3 ± 11.3	30.0 ± 12.7	31.3 ± 13.3
Disease Extension	Ulcerative Colitis	Proctitis	6 (10.34%)	3 (9.1%)	0 (0%)
		Left Colitis	23 (39.65%)	8 (24.2%)	4 (26.6%)
		Pancolitis	5 (8.62%)	6 (18.2%)	2 (13.3%)
	Crohn's Disease	L1	11 (18.97%)	7 (21.2%)	3 (20.0%)
		L2	6 (10.34%)	4 (12.1%)	2 (13.3%)
		L3	7 (12.07%)	5 (15.2%)	4 (26.6%)
Surgery, n (%)	No		34 (58.6%)	17 (51.5%)	8 (53.3%)
	Yes		24 (41.4%)	16 (48.5%)	7 (46.7%)
Therapy, n (%)	None		10 (17.2%)	4 (12.1%)	1 (6.7%)
	NSAIDS		20 (34.5%)	7 (21.2%)	5 (33.3%)
	Immunosuppressive medications		11 (19.0%)	8 (24.2%)	1 (6.7%)
	TNF inhibitors		14 (24.1%)	11 (33.3%)	5 (33.3%)
	Poli-therapy		3 (5.17%)	3 (9.1%)	3 (20.0%)

followed a year of treatment with antidepressants, the following nonparametric tests were used, given the small size of the sample: in the study of dichotomous variables, we used the Cochran Q test, a procedure for testing if the proportions of 3 or more dichotomous variables are equal in some population; to compare the comparison of continuous and ordinal variables, we used the Friedman test. Values of $p \leq 0.05$ were considered significant. The statistical analysis was carried out by using the SPSS program version 24 (IBM corp., 2016).

Results

Description of the Sample

In the sample of 170 IBD patients, 58 (34,1%) scored positively for the presence of depressive or mood symptoms (HADS score) and thus met the study inclusion criteria. Of the 58 patients recruited, 24 (41,1%) were suffering from CD and 34 (58,5%) from UC. Completed psychiatric diagnostic procedure 33 patients (17 UC, 16CD), equal to 19,4% of all the sample, were diagnosed with an anxiety or mood disorder (according to DSM-5 and ICD10 diagnostic criteria and underwent an antidepressant therapy: 16 patients (48.5%) with Major Mood Disorder (MMD), 5 (15.2%) Persistent Depressive Disorder (PDD), 8 (24.2%) with Depressive Anxioux Syndrome (DAS –according with ICD10) and 4 (12.1%) with panic disorder (PD). Only 15 patients (45,4% undergoing a treatment with antidepressant) completed all questionnaires during the year of follow-up. Side smallness single diagnostic subtypes, with prevalence of depressive disorders, we will appointed summarised from now as a group of patients IBD with affective disorders comorbidity.

Table 1 shows the socio-demographic characteristics of the sample.

Table 2 shows the clinical characteristics of the sample concerning IBD diagnosis, characteristics and treatment.

Table 3 shows the psychiatric diagnosis and relative treatment of the sample.

Anxious-depressive symptoms severity in patients with or without affective disorders

The mean severity scores of the total sample measured were 17.58±8.91 for HAM-A (moderate anxiety), and 15.34±7.80 for HAM-D (moderate depression). The sample diagnosed with an anxious or depressive disorder showed significantly higher severity scores, with a mean of 19.88±7.52 for HAM-A (moderate anxiety) ($t_{(56)}$=–4.5, p=0.001), and a mean of 17.31±6.52 for

Tab. 3. Psychiatric diagnosis and psychopharmacological treatments

Diagnosis DSM5 – ICD10	baseline (n 33)	%	12 months (n 15)	%
MDD	16	48.5	8	53.3
PDD	5	15.2	2	13.3
DAS	8	24.2	3	20.0
PD	4	12.1	2	13.3
AD therapy SSRI-SNRI				
Sertraline	15	45.5	10	66.7
Citalopram	3	9.1	1	6.7
Paroxetine	4	12.1	1	6.7
Fluoxetine	2	6.1	1	6.7
Duloxetine	7	21.2	2	13.3

Tab. 4. Mean anxiety and depression scores in n participants with and without affettive comorbidity the HAM-D and HAM-A scales

	No affective comorbidity (n=25)	With affective comorbidity (n=33)	Total sample (n=58)	$t_{(56)}$	*p*
HAM-D	4.83 ± 5.61	17.31 ± 6.52	15.34 ± 7.80	- 4.40	0.001
HAM-A	5.33 ± 5.21	19.88 ± 7.52	17.58 ± 8.91	- 4.52	0.001

HAM-D (moderate depression) ($t_{(56)}$=–4.4, p=0.001). The mean scores of anxious and depressive symptoms in the patients without a psychiatric diagnosis were subthreshold (HAM-A: mean=5.33±5.21, HAM-D: mean=4.83±5.61). The results are shown table 4.

Clinical and psychometric differences between IBD patients with or without an anxiety or mood disorder

A significantly higher proportion of patients in the sample with affective disorders showed increased diarrheal discharges than the group without it (66% vs. 40%, $X^2_{(4)}$=4.09, p=0.04). No significant differences emerged regarding rectal bleeding, abdominal pain, localization of the disease and the ongoing therapy for IBD, as shown in table 5.

Table 6 shows the scores obtained by the samples in the subdomains of the SCL90R.

The group with affective comorbidity presented significantly higher scores in anxiety domains than the sample without affective comorbidity. No significant differences in other domains were observed.

The analysis of the coping strategies in the two groups evaluated with the Brief-COPE scale revealed that the sample with an anxiety or mood disorder had a significant lower levels of "positive reframing" (4.45±1.41 vs. 5.32±1.72, $t_{(56)}$=2.08, p=0.042), "use of instrumental support" (4.40±1.83 vs. 5.43±1.99, $t_{(56)}$=2.07, p=0.043), and "use of emotional support" strategy (4.01±1.52 vs. 4.92±1.92, $t_{(56)}$=2.00, p=0.05) compared to to the population without psychiatric comorbidity. No other significant differences were observed.

The perception of the health status of IBD patients was studied with the SF-36 psychometric test. The patients with an anxiety or mood disorder showed significantly lower scores in the "Vitality" domain, (31.77±20.20 vs. 54.0±20.43, $t_{(56)}$=2.27, p=0.03), "General Health Perception" (29.87±14.10 vs. 44.80±22.30, $t_{(56)}$=2.28, p=0.05) and "Mental Health" (43.71±21.60 vs. 64.01±16.72, $t_{(56)}$=1.99, p=0.05). No other significant differences were observed.

Variation of IBD and psychiatric symptoms in patients undertaking an antidepressant therapy

In the 15 patients undergoing therapy and having completed one full year of diagnostic follow-up, the depressive and anxious symptomatology significantly decreased over time, as measured through the HAM-A (6.3±4.6 at 12 months vs. 25.6±8.1 at T0, $X^2_{(4)}$=33.90, p= 0.001) and HAM-D (21.5±47.4 at 12 months vs. 5.5±4.8 at T0, $X^2_{(4)}$=33.90, p=0.001). The proportion of patients complaining diarrhoea significantly reduced at he end of follow up (66% at T0 vs 33% at 12 months, $X^2_{(4)}$=16.02, p=0.003). No significant changes in prevalence of abdominal pain or rectal bleeding was observed. Extensive results shown in table 7.

Discussion

In our outpatient sample, a high prevalence of anxious and depressive symptoms was confirmed, in line with available literature. Moreover, in those presenting anxious or depressive symptoms, a high prevalence of anxiety and mood disorders was found, confirming the high prevalence of these disorders among patients with IBD (Fuller-Thomson *et al.* 2015; Mikocka-Walus *et al.* 2016; Porcelli *et al.* 1995; Tribbick *et al.* 2015).

Tab. 5. Comparative prevalence of gastrointestinal symptoms between the sample with an affective comorbidity and the sample without it

		No affective comorbidity (n=15)	With affective comorbidity (n=33)	Total sample (n=58)	$X^2_{(4)}$	*p*
Frequency of bowel movements (evacuation) n (%)	Regular	15 (60%)	11 (33.3%)	26 (44.8%)	4.09	0.043
	Increased	7 (40%)	22 (66.6%)	32 (55.2%)		
Abdominal pain, n (%)	No	19 (76%)	21 (63.6%)	40 (68.9%)	1.016	0.31
	Yes	6 (14%)	12 (36.4%)	18 (31.0%)		
Rectal bleeding, n (%)	No	19 (76%)	23 (69.7%)	42 (72.4%)	0.283	0.59
	Yes	6 (24%)	7 (30.3%)	16 (27.6%)		

In this population, HAM-D and HAM-A scores were significantly higher than in the general IBD sample. With regard to psychopathological dimensions, only that of anxiety was found to be significantly more represented in the population with an anxiety or mood disorder, while no significant differences emerged in any of the other psychopathological dimensions. We would have expected to find a significant difference between the samples also in the domain of depression, at the very least, given that the two populations showed significant different levels of anxiety and depression while tested with the HAM-A and HAM-D scales. Previous studies found high SCL-90R scores in IBD patients (Piacentino *et al.* 2019); another study found higher SCL-90R scores in active-disease patients compared with IBD patients with a disease in remission (Leone *et al.* 2019). While our study excluded IBD patients with active phase disease, we found high SCL-90R scores even in non-affective patients, in particular in the depression, OCD, somatization and sleep disorders domains. IBD patients tend to have high levels of personal distress and physical limitations, even when a clear-cut psychiatric diagnosis cannot be made. While the SCL-90R is an useful scale to highlight the presence of psychopathological symptoms in the general population, it might not possess the same sensibility and specificity when utilized within an IBD population.

Previous studies on the general IBD population found lower levels of quality of life measures in these patients (Bulut & Törüner 2019; Knowles *et al.* 2018a; Knowles *et al.* 2018b). Specifically, fatigue, as measured in the Vitality subscale of SF-36, is a common complaint among IBD patients (Farrell *et al.* 2020; Iglesias-Rey *et al.* 2012) and has been the target of various treatments in time (Farrell *et al.* 2020). Our study found that IBD patients with anxiety-depressive comorbidities have significantly lower levels of vitality, general health perception, and mental-health than their non-affective counterparts. High levels of anxious and depressive symptoms in IBD patients were found to be associated with worse scores in all the SF-36 dimensions, including vitality (Iglesias-Rey *et al.* 2014; Nordin *et al.* 2002). With regard to this dimension, the symptoms of depression and anxiety could not only layer upon those of IBD to reduce the levels of energy of these patients, but could also influence their health self-perception. Moreover, the presence of anxiety and depressive symptoms

Tab. 6. Comparative analysis of SCL-90 scale scores

Items SCL-90R	No affective comorbidity (n=25)	With affective comorbidity (n=33)	Total sample (n=58)	$t_{(56)}$	*p*
Somatization	1.11 ± 0.71	1.5 ± 0.92	1.35 ± 0.85	-1.84	0.10
Obsessive compulsive	1.38 ± 0.62	1.49 ± 0.90	1.44 ± 0.83	-0.49	0.66
Interpersonal sensitivity	1.11 ± 0.74	1.04 ± 0.72	1.07 ± 0.75	0.29	0.97
Depression	1.37 ± 0.73	1.66 ± 0.94	1.54 ± 0.86	-1.23	0.18
Anxiety	1.07 ± 0.60	1.35 ± 0.82	1.24 ± 0.73	**3.87**	**0.049**
Hostility	0.91 ± 0.61	0.97 ± 0.83	0.95 ± 0.76	-0.29	0.62
Phobic anxiety	0.54 ± 0.43	0.83 ± 0.92	0.71 ± 0.79	-1.35	0.13
Paranoid ideation	1.14 ± 0.64	1.00 ± 0.84	1.06 ± 0.73	0.70	0.16
Psychoticism	0.58 ± 0.40	0.72 ± 0.50	0.66 ± 0.48	-1.08	0.51
Sleep disorders	1.68 ± 1.42	1.59 ± 1.30	1.63 ± 1.34	0.26	0.77
GSI	1.07 ± 0.52	1.23 ± 0.71	1.16 ± 0.61	0.91	0.79

Tab. 7. Mean values and standard deviations of HAM-D and HAM-A scores and gastrointestinal symptoms prevalence at follow-up time points (T0 being the beginning of the study, T0 through T12 representing 3-6-9-12 months from T0).

		T0	T1	T3	T6	T12	P	$X^2_{(4)}$
HAM-A mean ± SD		25.6 ± 8.1	12.3 ± 7.1	7.4 ± 4.5	5.2 ± 3.3	6.3 ± 4.6	0.001	33.90
HAM-D means ± SD		21.5 ± 7.4	11.7 ± 7.9	7.1 ± 3.9	4.8 ± 4.1	5.5 ± 4.8	0.001	33.92
Frequency of bowel movements n (%)	Regular	5 (33.3%)	11 (73.3%)	12 (80%)	10 (66.6%)	10 (66.6%)	0.003	16.02
	Increased	10 (66.6%)	4 (26.6%)	3 (20%)	5 (33.3%)	5 (33.3%)		
Abdominal pain, n (%)	Absent	10 (66.6%)	10 (66.6%)	12 (80%)	9 (60%)	9 (60%)	0.71	2.14
	Present	5 (33.3%)	5 (33.3%)	3 (20%)	6 (40%)	6 (40%)		
Bleeding, n (%)	Absent	11(73.3%)	13 (86.6%)	15(100%)	15 (100%)	13 (86.6%)	0.09	8.01
	Present	4 (26.6%)	2 (13.3%)	0 (0%)	0 (0%)	2 (13.3%)		

The variation of gastrointestinal symptomatology in time was studied with the application of the Cochran Q Test, while that of HAM-D and HAM-A with the Friedman test.

in the patients with IBD-affective comorbidity easily explain the lower scores in the mental health subdomain of SF-36 found in this group.

The sample with an anxiety or mood disorder presented significant lower values in several coping strategies ("positive restructuring", "use of instrumental support", "use of emotional support").

This results aligns with the vast literature finding poorer coping mechanisms in affective patients, translated in the present study in a specific population which is also affected by IBD.

Given the disruptive impact of a chronic disease diagnosis, together with chronic, recurrent pain and the lifelong personal limitations that this imposes on many of these patients, it is reasonable to think that a reduced ability to positively frame one's situation (Roohafza *et al.* 2014), and to share one's burden with others, could worsen the perceived stress levels caused by the disease (Larsson *et al.* 2017), therefore increasing the risk to incur in a depressive episode or to exhibit anxious symptoms. On the other hand, the presence of an affective disorder could influence the patient's ability to cope positively with the intestinal disease, both because of the typical dysfunctional cognitions present in depression and anxious disorders, and because of the social isolation that these disorders cause.

Furthermore, previous studies on the impact of coping styles in IBD also found a positive association between anxiety and depression and passive coping (Crane & Martin 2004) and catastrophizing (Rhodes 2007), and a negative one with personal control (Curtis 2005). The finding that IBD-affective patients show a lesser capacity of positively restructure life events aligns with the cited studies, since this coping mechanism is antithetical to a catastrophizing attitude and it likely is a prerequisite for most active forms of coping, as well as with a perception of personal control.

Another study by some of the authors of this very manuscript previously found that Crohn Disease patients with depression had significantly lower levels of "positive restructuring", being in line with the present results, but higher levels of "use of instrumental support" and "use of emotional support" than the CD patients without depression (Viganò *et al.* 2016b), in contrast with the results of this study. This could be explained by the fact that the population studied in the former study was mainly only of CD patients with depressive, not anxious, symptoms, and could reflect both the different cognitive distortions and behavioral alterations present in depressive and anxiety disorders, and the different psychological profile of patients with UC versus CD, which has so far been only scarcely investigated. Another study indeed found that CD patients used significantly more emotion-focused coping than UC patients (Curtis 2005).

At the end of the diagnostic phase, patients were placed on antidepressant treatment. The molecule was chosen based on safety and low risk of side effects, as reported in literature (Cipriani *et al.* 2010; Iskandar *et al.* 2014). In the patients who completed one year of AD therapy, a significant improvement of psychopathological symptoms and reduction of evacuation frequency was observed. Since this symptom is non-specific and can be a manifestation of both IBD or anxiety, it is difficult to clearly define if its reduction was due to a direct effect of AD therapy on the pathogenesis of IBD symptoms or on the co-occurring anxiety and mood disorder (Turner & Kelly 2000).

In particular, the HAM-D and HAM-A scores and the frequency of discharges almost halved after the first month of treatment, and then presented a slower but progressive reduction until the third month. After that, the percentage of patients with increased discharge frequency increases from the third month onwards, but without ever reaching the initial levels. The HAM-D and HAM-A scores slightly increase after six month of treatment, while still remaining at subthreshold levels. These fluctuating trends in symptoms are char-

acteristic of IBD, with several studies finding a variation of the prevalence of anxiety and depression according to the stage of illness (Persoons *et al.* 2005; Porcelli *et al.* 1996).

As mentioned above, the frequency of discharges represents the functional symptom par excellence, characterized by an important psychic component, which is why it is typical of IBS and can be compared to anxious somatic symptoms. It also represents the most subjectively debilitating symptom of IBS, combined with urgency of evacuation. Patients often report concerns about leaving home, going to work or performing the simplest actions due to the fear of fecal incontinence and not finding available toilets in time. This leads to avoidance, work absenteeism and social isolation (Farrell & Savage 2012; Farrell *et al.* 2016; Sajadinejad *et al.* 2012). Gastroenterologists for some years have been prescribing antidepressants as collateral therapy for the reduction of functional symptoms in patients with chronic abdominal pain, irritable bowel syndrome and evacuation urgency. However, most remain skeptical about their possible central role in the treatment of IBD (Mikocka-Walus *et al.* 2007), although evidence in favor of the so-called "gut-brain axis" theory (Keefer & Kane 2017; Mayer *et al.* 2015) are increasingly richer. Further studies are needed to confirm the role of inflammation as a link between psychiatric pathology and IBD and to investigate the effects of psychotropic drugs on the pathogenesis and evolution of IBD. Our results support this role, since in our study antidepressant therapy has proven to be effective in reducing both the frequency of evacuation and anxiety-depressive symptoms. It's to be noted that while we found a statistical, positive effect of AD on gastrointestinal symptoms, we could not rule out the effect of stress or other contingent variables on the evolution of intestinal symptoms. A regression analysis taking into account the effect on the prognosis of other variables would be necessary to do this. A viable measure of social stressors to be adopted in further studies could be the Social Readjustment Rating Scale (SRRS). In this study though, the limited number of patients undergoing treatment would have made this type of analysis unfeasible (Roca *et al.* 2013).

The main limitations of this study are due to his retrospective naturalistic design, as well as the small sample size. While we collected relevant data concerning the clinical evolution of our in-treatment sample, only 15 of them completed the full battery of psychometric scales for the entire duration of the follow-up, and 12 (36%) patients dropped out before the 12-month deadline, making the following analysis of the data of little statistical significance.

In successive follow-up studies on this topic, we plan to implement a stricter control on the actual completion of all the required scales for the study. We do believe that, in any case, the results obtained from evaluating the effects of AD therapy on intestinal symptomatology, to be of practical clinical interest per se: this approach can easily be reproduced by non-psychiatrist clinicians such as gastroenterologists, general surgeons or GP's treating IBD-affective patients, without the need of administering the patients more complicated and specific forms of assessment, suchs as the SF-36.

Despite the stigma of psychiatric diagnosis and the subjective resistance of these patients to be treated by a psychiatrist, most of the subjects of the study expressed appreciation for the integrated approach they were evaluated and treated with and for the attention paid to their global health.

This study adds to the scientific evidence already present in literature which emphasizes the importance and usefulness of a multidisciplinary approach for the treatment of patients suffering from IBD. We also found that this approach, in addition to providing patients with a better care, allows for a better communication between the specialists involved.

The results obtained confirm and are consistent with the data present in literature on the topic of treatment with SSRI or SNRI antidepressants of IBD patients with a comorbid anxiety-depressive disorder. These drugs represent a valid therapeutic aid, acting both on the psychic and on the intestinal dimension. This conclusion demonstrates how IBD and anxiety-depressive symptoms are interconnected pathological entities.

Keypoints

- Anxious and depressive disorders are highly frequent among IBD patients.
- In IBD patients, the presence of an affective comorbidity is associated to an increased frequency of diarrheal discharges
- In IBD patients, the presence of anxiety or depressive disorders is associated with a reduced sense of vitality, and with lower scores in several coping mechanisms.
- In IBD-affective patients, one-year administration of AD therapy was shown to be effective in reducing both psychopathological symptoms, and the frequency of diarrheal evacuation.

REFERENCES

1 Abraham C & Cho JH (2009). Inflammatory bowel disease. *N Engl J Med.* **361**: 2066–2078.
2 American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders. Washington, DC Publisher, 5th ed.
3 Baumstarck K, Alessandrini M, Hamidou Z, Auquier P, Leroy T, Boyer L (2017). Assessment of coping: a new french four-factor structure of the brief COPE inventory. *Health Qual Life Outcomes.* **15**(1): 8.
4 Bernstein C.N, Hitchon A.C, Walld R. (2019). Increased Burden of Psychiatric Disorders in Inflammatory Bowel Disease, *Inflamm. Bowel Dis.* **25**(2): 360–368.
5 Bhamre R, Sawrav S, Adarkar S, Sakaria R, Bhatia SJ (2018). Psychiatric comorbidities in patients with inflammatory bowel disease. *Indian J Gastroenterol.* **37**(4): 307–312.
6 Brasileiro SV, Orsini MRCA, Cavalcante JA, Bartholomeu D, Montiel JM, Costa PSS, et al. (2016). Controversies Regarding the Psychometric Properties of the Brief COPE: The Case of the Brazilian-Portuguese Version COPE Breve. *PLoS One.* **11**(3): e0152233.

7 Bulut EA & Törüner M (2019). The influence of disease type and activity to sexual life and health quality in inflammatory bowel disease. *Turk J Gastroenterol.* **30**(1): 33–39.
8 Byrne G, Rosenfeld G, Leung Y, Qian H, Raudzus J, Nunez C, et al (2017). Prevalence of anxiety and depression in patients with inflammatory bowel disease. *Can J Gastroenterol Hepatol.* 6, Article ID 6496727.
9 Carver CS (1997). You want to measure coping but your protocol' too long: Consider the brief-cope. *Int J Behav Med.* **4**(1): 92–100.
10 Chan W, Shim HH, Lim MS, Sawadjaan FLB, Isaac SP, Chuah SW, et al (2017). Symptoms of anxiety and depression are independently associated with inflammatory bowel disease-related disability. *Digest Liver Dis.* **49**: 1314–1319.
11 Choi K, Chun J, Han K, Park S, Soh H, Kim J (2019). Risk of Anxiety and Depression in Patients with Inflammatory Bowel Disease: A Nationwide, Population-Based Study. *J Clin Med.* **8**(5): 654.
12 Cipriani A, La Ferla T, Furukawa TA, Signoretti A, Nakagawa A, Churchill R, et al (2010). Sertraline versus other antidepressive agents for depression - The Cochrane Library - Cipriani. *Cochrane Database Syst Rev.* **4**: CD006117.
13 Crane C & Martin M (2004). Social learning, affective state and passive coping in irritable bowel syndrome and inflammatory bowel disease. *Gen Hosp Psychiatry.* **26**(1): 50–58.
14 Curtis CE (2005). Disease activity, coping behavior, social support, and illness-related self-disclosure among persons with inflammatory bowel disease: a framework for quality of life. Diss Abstr Int B Sci Eng (Dissertation). Chicago (IL): DePaul University.
15 Daghaghzadeh H, Naji F, Afshar H, Sharbafchi MR, Feizi A, Maroufi M (2015). Efficacy of duloxetine add on in treatment of inflammatory bowel disease patients: A double-blind controlled study. *J Res Med Sci.* **20**(6): 595–601.
16 Derogatis LR, Lipman RS, Covi L (1973). SCL-90: an outpatient psychiatric rating scale--preliminary report. *Psychopharmacol Bull.* **9**(1): 13–28.
17 Farrell D & Savage E (2012). Symptom burden: A forgotten area of measurement in inflammatory bowel disease. *Int J Nurs Pract.* **18**(5): 497–500.
18 Farrell D, Artom M, Czuber-Dochan W, Jelsness-Jørgensen LP, Norton C, Savage E (2020). Interventions for fatigue in inflammatory bowel disease. *Cochrane Database Syst Rev.* **4**(4): CD012005.
19 Farrell D, Mccarthy G, Savage E (2016). Self-reported symptom burden in individuals with inflammatory bowel disease. *J Crohn's Colitis.* **10**(3): 315–322.
20 Ford AC, Lacy BE, Harris LA, Quigley EMM, Moayyedi P (2019). Effect of antidepressants and psychological therapies in irritable bowel syndrome. *Am J Gastroenterol.* **114**(1): 21–39.
21 Frolkis AD, Vallerand IA, Shaheen AA, Lowerison MW, Swain MG, Barnabe C (2018). Inflammatory bowel disease depression increases the risk of inflammatory bowel disease, which may be mitigated by the use of antidepressants in the treatment of depression. *Gut.* **68**(9): 1606–1612.
22 Fuller-Thomson E, Lateef R, Sulman J (2015). Robust association between inflammatory bowel disease and generalized anxiety disorder: findings from a nationally representative Canadian study. *Inflamm Bowel Dis.* **21**: 2341–2348.
23 Goodhand JR, Greig FIS, Koodun Y, McDermott A, Wahed M, Langmead L, Rampton DS (2012). Do antidepressants influence the disease course in inflammatory bowel disease? A retrospective case-matched observational study. *Inflamm Bowel Dis.* **18**(7): 1232–1239.
24 Graff LA, Walker JR, Lix L, Clara I, Rawsthorne P, Rogala L, et al (2006). The relationship of inflammatory bowel disease type and activity to psychological functioning and quality of life. *Clin Gastroenterol Hepatol.* **4**: 1491– 1501.
25 Graff LA, Walker JR, Bernstein CN (2009). Depression and anxiety in inflammatory bowel disease: A review of comorbidity and management. *Inflamm Bowel Dis.* **15**(7): 1105–1118.
26 Hallit S, Haddad C, Hallit R, Akel M, Obeid S, Haddad G, et al (2019). Validation of the Hamilton Anxiety Rating Scale and State Trait Anxiety Inventory A and B in Arabic among the Lebanese population. *Clin Epidemiol Glob Health.* **7**(3): 464–470.
27 Hamilton M (1959). The assessment of anxiety states by rating. *Br J Med Psychol.* **32**(1): 50–5.
28 Hamilton M (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry.* **23**(1): 56–62.
29 Hopkins CWP & Moulton CD (2016). The prevalence of alexithymia in inflammatory bowel disease: a systematic review and meta-analysis. *Journal of Crohn's and Colitis.* **10**: 443.
30 Iglesias-Rey M, Barreiro-de Acosta M, Caamaño-Isorna F, Vázquez Rodríguez I, Lorenzo González A, Bello-Paderne X, et al (2012). Influence of alexithymia on health-related quality of life in inflammatory bowel disease: are there any related factors? *Scand J Gastroenterol.* **47**(4): 445–53.
31 Iglesias-Rey M, Barreiro-de Acosta M, Caamaño-Isorna F, et al (2014). Psychological factors are associated with changes in the health-related quality of life in inflammatory bowel disease. *Inflamm Bowel Dis.* **20**(1): 92–102.
32 Ishak WW, Pan D, Steiner AJ, Feldman E, Mann A, Mirocha J, et al (2017). Patient-reported outcomes of quality of life, functioning, and GI/psychiatric symptom severity in patients with Inflammatory Bowel Disease (IBD). *Inflamm Bowel Dis.* **23**: 798–803.
33 Iskandar HN, Cassell B, Kanuri N, Gyawali CP, Gutierrez A, Dassopoulos T (2014). Tricyclic antidepressants for management of residual symptoms in inflammatory bowel disease. *J Clin Gastroenterol.* **48**(5): 423–429.
34 Jenkinson C, Coulter A, Wright L (1993). PAPERS Short form 36 (SF 36) health survey questionnaire: normative data for adults of working age. *BMJ.* **306**: 1437–1440.
35 Jostins L (2012). Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* **491**: 119–24.
36 Katon WJ (2011). Epidemiology and treatment of depression in patients with chronic medical illness. *Dialogues Clin Neurosci.* **13**: 7–23.
37 Keefer L & Kane SV (2017). Considering the bidirectional pathways between depression and IBD: recommendations for comprehensive IBD care. *Gastroenterol Hepatol.* **13**(3): 164–169.
38 Knowles SR, Graff LA, Wilding H, Hewitt C, Keefer L, Mikocka-Walus A (2018a). Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses Part I. *Inflamm Bowel Dis.* **24**(4): 742–751.
39 Knowles SR, Keefer L, Wilding H, Hewitt C, Graff LA, Mikocka-Walus A (2018b). Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses Part II. *Inflamm Bowel Dis.* **24**(5): 966–976.
40 La Barbera D, Bonanno B, Rumeo MV, Alabastro V, Frenda M, Massihnia E, et al (2017). Alexithymia and personality traits of patients with inflammatory bowel disease. *Sci Rep.* **7**: 1–11.
41 Larsson K, Lööf L, Nordin K (2017). Stress, coping and support needs of patients with ulcerative colitis or Crohn's disease: a qualitative descriptive study. *J Clin Nurs.* **26**(5-6): 648–657.
42 Leone D, Gilardi D, Corrò BE, Menichetti J, Vegni E, Correale C, et al (2019). Psychological Characteristics of Inflammatory Bowel Disease Patients: A Comparison Between Active and Nonactive Patients. *Inflamm Bowel Dis.* **25**(8): 1399–1407.
43 Maconi G, Gridavilla D, Viganò C, Scurti R, Asthana AK, Furfaro F, et al (2014) Perianal disease is associated with psychiatric comorbidity in crohn's disease in remission" *Int J Colorectal Dis.* **29**: 1285–1290.
44 Maes M (2001). The immunoregulatory effects of antidepressants. *Hum Psychopharmacol Clin Exp.* **16**(1): 95–103.
45 Maier W, Buller R, Philipp M, Heuser I (1988). The Hamilton Anxiety Scale: reliability, validity and sensitivity to change in anxiety and depressive disorders. *J Affect Disord.* **14**(1): 61–68.
46 Mardini HE, Ki KE, Wilson JW (2004). Crohn's Disease: A Two-Year Prospective Study of the Association Between Psychological Distress and Disease Activity. *Dig Dis Sci.* **49**(3): 492–497.
47 Mayer EA, Tillisch K, Gupta A (2015). Gut/Brain Axis and the Microbiota. *J Clin Invest.* **125**(3): 926–938.
48 McCombie RT, Mulder, Gearry RB (2013). How IBD patients cope with IBD: A systematic review. *J Crohn's Colitis.* **7**(2): 89–106.
49 Mikocka-Walus A, Pittet V, Rossel JB, von Känel R (2016). Swiss IBD Cohort Study Group. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin Gastroenterol Hepatol.* **14**(6): 829–835.

50 Mikocka-Walus A, Turnbull DA, Moulding NT, Wilson IG, Andrews JM, Holtmann GJ (2007). "It doesn't do any harm, but patients feel better": a qualitative exploratory study on gastroenterologists' perspectives on the role of antidepressants in inflammatory bowel disease. *BMC Gastroenterol.* **7**(1): 1–6.

51 Mittermaier C, Dejaco C, Waldhoer T, Oefferlbauer-Ernst A, Miehsler W, Beier M, et al (2004). Impact of Depressive Mood on relapse in Patients with Inflammatory Bowel Disease: A Prospective 18-Month Follow-Up Study. *Psychosom Med.* **66**(1): 79–84.

52 Monsén U, Sorstad J, Hellers G, Johansson C (1990). Extracolonic diagnoses in ulcerative colitis: an epidemiological study. *Am J Gastroenterol*. **85**: 711–716.

53 Moradkhani A, Beckman LJ, Tabibian JH (2013). Health-related quality of life in inflammatory bowel disease: psychosocial, clinical, socioeconomic, and demographic predictors. *J Crohns Colitis.* **7**: 467–473.

54 Nahon S, Lahmek P, Durance C, Olympie A, Lesgourgues B, Colombel JF, et al (2012). Risk Factors of Anxiety and Depression in Inflammatory Bowel Disease. *Inflamm Bowel Dis*. **18**(11): 2086–2091.

55 Nordin K, Påhlman L, Larsson K, Sundberg-Hjelm M, Lööf L (2002). Health-Related Quality of Life and Psychological Distress in a Population-based Sample of Swedish Patients with Inflammatory Bowel Disease. *Scand J Gastroenterol.* **37**(4): 450–457.

56 Oswald J, Salemi S, Michel BA, and Sprott H (2008). Use of the Short-Form-36 Health Survey to detect a subgroup of fibromyalgia patients with psychological dysfunction. *Clin Rheumatol.* **27**(7): 919–921.

57 Persoons P, Vermeire S, Demyttenaere K, Fischler B, Vandenberghe J, Van Oudenhove L, et al (2005). The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. *Aliment Pharmacol Ther.* **22**(2): 101–110.

58 Piacentino D, Cesarini M, Badiali D, Pallotta N, Biondi M, Corazziari ES (2019). The central role of psychopathology and its association with disease severity in inflammatory bowel disease and irritable bowel syndrome. *Riv Psichiatr.* **54**(2): 75–83.

59 Porcelli P, Leoci C, Guerra V (1996). A prospective study of the relationship between disease activity and psychologic distress in patients with inflammatory bowel disease. *Scand J Gastroenterol.* **31**(8): 792–796.

60 Porcelli P, Zaka S, Leoci C, Centonze S, Taylor GJ (1995). Alexithymia in inflammatory bowel disease. A case-control study. *Psychother Psychosom.* **64**: 49–53.

61 Rhodes AR (2007). Quality of life issues for people with IBD: an exploratory study to investigate the relationship of coping skills, social support and negative social interactions to anxiety and depression for people with IBD. *Diss Abstr Int B Sci Eng* (Dissertation). Columbus (OH): Ohio State University.

62 Roca M, Gili M, Garcia-Campayo J, Armengol S, Bauza N, García-Toro M (2013). Stressful life events severity in patients with first and recurrent depressive episodes. *Soc Psychiatry Psychiatr Epidemiol.* **48**(12): 1963–1969.

63 Roohafza HR, Afshar H, Keshteli AH, Mohammadi N, Feizi A, Taslimi M, et al (2014). What's the role of perceived social support and coping styles in depression and anxiety? *J Res Med Sci.* **19**(10): 944–949.

64 Sajadinejad MS, Asgari K, Molavi H, Kalantari M, Adibi P (2012). Psychological Issues in Inflammatory Bowel Disease: An Overview. *Gastroenterol Res Pract.* **2012**: 1–11.

65 Scott KM, Bruffaerts R, Tsang A, Ormel J, Alonso J, Angermeyer MC, et al (2007). Depression-anxiety relationships with chronic physical conditions: results from the World Mental Health Surveys. *J Affect Disord.* **103**: 113–120.

66 Severs M, Mangen MJ, Fidder HH, van der Valk ME, van der Have M, van Bodegraven AA, et al (2017). Clinical predictors of future nonadherence in inflammatory bowel disease. *Inflamm Bowel Dis.* **23**: 1568–1576.

67 Sharp S (2015). The Hamilton Rating Scale for Depression. *Occup Med (Chic. Ill).* **65**(4): 340.

68 SPSS Statistics for Windows, Version 24.0. (2016). Armonk, NY: IBM Corp.

69 Thompson E (2015). Hamilton Rating Scale for Anxiety (HAM-A). *Occup. Med. (Chic. Ill).* **65**(7): 601–601.

70 Trajković G, Starčević V, Latas M, Leštarević M, Ille T, Bukumirić Z et al (2011). Reliability of the Hamilton Rating Scale for Depression: A meta-analysis over a period of 49 years. *Psychiatry Res*. **189**: 1–9.

71 Tribbick D, Salzberg M, Ftanou M, Connell WR, Macrae F, Kamm MA, et al (2015). Prevalence of mental health disorders in inflammatory bowel disease: An Australian outpatient cohort. *Clin Exp Gastroenterol.* **8**: 197–204.

72 Turner J & Kelly B (2000). Emotional dimensions of chronic disease. *West J Med.* **172**(2): 124–128.

73 Uguz A, Akman C, Kucuksarac S, Tufekci O (2009). Anti-tumor necrosis factor-α therapy is associated with less frequent mood and anxiety disorders in patients with rheumatoid arthritis. *Psychiatry Clin Neurosci.* **63**(1): 50–55.

74 Viganò C, Truzoli R, Beltrami M, Marinaccio PM, Bosi F, Maconi G, et al (2016a). Prevalence of anxious and depressive symptoms, and coping strategies as risk factors in Crohn's disease outpatients in clinical remission. *Act Nerv Super Rediviva.* **58**(4): 118–122.

75 Viganò C, Calzolari R, Marinaccio PM, Bezzio C, Furfaro F, Ba G, et al (2016b). Unrevealed Depression Involves Dysfunctional Coping Strategies in Crohn's Disease Patients in Clinical Remission. *Gastroenterol Res Pract.* 1–7.

76 Viganò CA, Beltrami MM, Bosi MF, Zanello RL, Valtorta M, Maconi G (2018). Alexithymia and Psychopathology in Patients Suffering from Inflammatory Bowel Disease: Arising Differences and Correlations to Tailoring Therapeutic Strategies. *Front Psychiatry.* **9**: 324.

77 Walker JR, Ediger JP, Graff LA, Greenfeld JM, Clara I, Lix L, et al (2008). The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *Am J Gastroenterol.* **103**: 1989–1997.

78 Ware JJ & Sherbourne C (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. - PubMed – NCBI. *Med Care.* **30**(6): 473–483.

79 Yanartas O, Kani HT, Bicakci E, Kilic I, Banzragch M, Acikel C, et al (2016). The effects of psychiatric treatment on depression, anxiety, quality of life, and sexual dysfunction in patients with inflammatory bowel disease. *Neuropsychiatr Dis Treat.* **12**: 673–683.

80 Zhang Y, Qu B, Lun SS, Guo Y, Liu J (2012). The 36-item short form health survey: reliability and validity in Chinese medical students. *Int J Med Sci.* **9**(7): 521–526.