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| CORE TIP | Bipolar patients with depressive symptoms, but not with anxiety symptoms, reported more gastrointestinal (GI) symptoms than control subjects. Unexplained GI-symptoms in bipolar patients should be seriously considered to suffer from depression and receive adequate treatment. |
| KEY WORDS | Anxiety; Bipolar disorder; Brain-Gut axis; Depression; Dyspepsia; Functional gastrointestinal disorder; Gastrointestinal Symptom Rating Scale- irritable bowel syndrome; Irritable bowel syndrome; Hospital Anxiety and Depression Scale; Stress |
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**Case Control Study**

Association between gastrointestinal symptoms and affectivity in patients with bipolar disorder

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**Abstract**

**AIM**

To study if anxiety, depression and experience of stress are associated with gastrointestinal (GI) symptoms in patients with bipolar disorder.

**METHODS**

A total of 136 patients with bipolar disorder (mean age 49.9 years; 61% women) and 136 controls from the general population (mean age 51.0 years; 60% women) were included in the study. GI symptoms were assessed with The Gastrointestinal Symptom Rating Scale-irritable bowel syndrome (GSRS-IBS), level of anxiety and depression with The Hospital Anxiety and Depression Scale (HADS) and stress-proneness with Perceived Stress Questionnaire. Over a ten year period, all visits in primary care were retrospectively recorded in order to identify functional GI disorders.

**RESULTS**

In subjects with low total HADS-score, there were no significant differences in GI-symptoms between patients and controls (GSRS-IBS 7.0 *vs* 6.5, *P* = 0.513). In the patients with bipolar disorder there were significant correlations between all GSRS and HADS subscores for all symptom clusters except for “constipation” and “reflux”. Factors associated to GI symptoms in the patient group were female sex (adjusted OR = 2.37, 95%CI: 1.07-5.24) and high HADS-Depression score (adjusted OR = 3.64, 95%CI: 1.07-12.4). These patients had also significantly more visits for IBS than patients with low HADS-Depression scores (29% *vs* 8%, *P* = 0.008). However, there was no significant differences in consulting behaviour for functional GI disorders between patients and controls (25% *vs* 17%, *P* = 0.108).

**CONCLUSION**

Female patients and patients with high HADS depression score reported significantly more GI symptoms, whereas patients with low HADS scores did not differ from control subjects.

**Key words:** Anxiety; Bipolar disorder; Brain-Gut axis; Depression; Dyspepsia; Functional gastrointestinal disorder; Gastrointestinal Symptom Rating Scale- irritable bowel syndrome; Irritable bowel syndrome; Hospital Anxiety and Depression Scale; Stress

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**Core tip:** Bipolar patients with depressive symptoms, but not with anxiety symptoms, reported more gastrointestinal (GI) symptoms than control subjects. Unexplained GI-symptoms in bipolar patients should be seriously considered to suffer from depression and receive adequate treatment.

**INTRODUCTION**

Affective disorders or affective symptoms such as depression and anxiety are common in those who seek help for functional gastrointestinal (GI) complaints[1]. Studies concerning the relationship between anxiety/depression and GI symptoms might be biased by a higher health care utilization that comes with psychological comorbidity[2,3]. To study the temporal relationship between the onset of gut symptoms and the onset of affective symptoms is difficult because of the insidious onset and fluctuating course of both affective and functional GI disorders[3,4]. Most studies that aim to characterize the relationship between bowel disorders and anxiety/depression are performed on patients from gastroenterology units. These patients often have longstanding and disabling gut symp­toms with negative consequences on quality of life which in the long run may have an impact on mood. Therefore, a different approach for studying how affective syndromes influence the bowel and brain-gut interactions is to set the starting point at the psychiatric patients. Accordingly, there are relatively few studies using this approach[5]. In a large group of patients with unipolar depression, we have previously described that GI symptoms were common and related to symptoms of anxiety and depression[6]. Patients with unipolar depression have more pain, including abdominal pain, which in part correlates with the severity of the depressive mood, and patients with unipolar depression show a higher health care utilization for symptoms not denoted as “psychiatric”[5-9].

Bipolar disorder, including different subtypes such as bipolar disorder 1 and 2, is a common condition with reported life time prevalence in the population estimated at 2.4%[10]. Furthermore, in the last decade bipolar disorder is more described as a chronic, progressive disorder with significant residual symp­toms between episodes of depression and mania/hypomania rather than classically cyclical illness[11]. It is estimated that bipolar disorder patients suffer from affective symptoms 50% of the time even if they are appropriately treated and are receiving mood stabilizing medication. The cost of total health care for patients with bipolar disorder is estimated at two to four times higher than for age- and sex matched controls[12]. In contrast to patients with unipolar depression, there are little published data concerning functional GI symptoms in patients with bipolar disorder.

The primary aim of this study was to compare the prevalence of GI symptoms in patients with bipolar disorder versus controls, and to determine the extent to which symptoms of anxiety/depression/stress and GI symptoms correlates in patients with an established bipolar disorder. A secondary aim was to determine if other factors than affectivity are associated to GI symptoms in patients with bipolar disorder.

**MATERIALS AND METHODS**

***Study participants***

Outpatients with a bipolar type 1 or type 2 diagnoses were considered for participation in the study, which is part of the multiple-outcome research project, the Umeå Bipolar project. The patients were treated at a specialized outpatient affective unit at Umeå University Hospital. The diagnoses were made according to DSM-IV criteria[13]. General exclusion criteria were dementia, mental retardation, relatedness as well as any other feature that would compromise the ability to fulfil the study protocol such as not having Swedish as a mother tongue, several visual or auditory handicaps. Pertaining to more specific exclusion criteria of the present study, all subjects with abdominal surgery within three months before and after the survey, and all with established GI diseases, hepatic and renal diseases were excluded. Subjects on beta blockers, calcium antagonists, statines, antidepressants, pain medication including non-steroidal anti inflammatory medications were not excluded. Of 149 patients with bipolar disorder, 136 patients (88 bipolar type 1 and 48 bipolar type 2) between 20 and 84 years of age fulfilled the inclusion criteria and accepted participation. All patients were on stable medical treatment for three months prior to the study.

The control sample consisted of 136 age- and sex-matched subjects from a sub study of the Betula project (*n* = 299). The Betula project is a large multiple-outcome study focused at exploring memory, health and aging in the general population. All participants were randomly selected from the population registry of the same region as the patient sample (the Umeå region, northern Sweden) and have been shown to be representative of the general population[14]. The same exclusion criteria for the patients were applied to the control sample. The controls who took medications were likewise on stable treatment at least three month prior to the study.

***Questionnaires***

The Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS) is a validated self-assessment instrument to assess symptoms of irritable bowel syndrome (IBS)[15]. The GSRS-IBS questionnaire includes 13 items, each using a Likert scale (0-6 points). The items are grouped into symptom clusters: Abdominal pain (two items), bloating (three items), constipation (two items), diarrhoea (four items) and satiety (two items). There is currently not a defined cut-off level for having IBS in the GSRS-IBS questionnaire. Therefore, to explore the relationship between IBS-like symptoms with other factors in patients with bipolar disorder we used the median total GSRS-IBS score (the sum of all 13 items score) for the patients. In addition, but not included in the total GSRS-IBS score, we used five questions from the former Gastrointestinal Symptom Rating Scale (GSRS), that concern symptoms of gastroesophagal reflux (two items) and dyspepsia (three items)[16].

The Hospital Anxiety and Depression Scale (HADS), developed by Zigmond and Snaith in 1983[17], is a highly sensitive instrument to screen for symptoms of anxiety and depression among patients with somatic diseases. It consists of 7 items each for anxiety and depression, each using a 4-point Likert scale (0-3 points). We used the HADS scale because it has high sensitivity in detecting symptoms of anxiety and depression, it is well validated, and it is simple to fill in, which facilitates a higher response rate[18,19]. The accepted cut-off level of 8 points or more for the depression part of HADS (HADS-D) was used to define patients suffering from depression and the cut off level of 9 points or more was used to define patients suffering from anxiety (HADS-A).

The Perceived Stress Questionnaire (PSQ) was developed to measure general stress perceived during the past year and emphasizes cognitive perceptions more than emotional states or specific life events[20].The PSQ consist of 30 items using a 4-point Likert scale (0-3 points). A PSQ index, varying from 0 (the lowest level) to 1 (the highest level) is calculated by dividing the total raw score with 90[20]. We used the estimated PSQ index of > 0.34 to define moderate level of perceived stress[21].

***Medical records***

After written consent from the subjects who responded to the questionnaires, records of primary care, surgery (including endoscopy unit) and infection clinics from 1999-2009, were searched twice for exclusion criteria (see study participants). The Swedish health care system includes a primary care health system with general physicians taking care of all initial referrals (except emergencies). Therefore, all patients who attend the gastroenterology out-patient clinic are initially referred by a general physician within the primary care. Blinded by the result of GSRS-IBS and HADS questionnaires, the records of primary care health centres were investigated twice to define consulters for IBS and any functional bowel disorders. Consulters for GI symptoms were defined by diagnosis of a functional bowel disorder as judged by their general physician or symptoms according to ROME Ⅲ criteria[22].

***Statistical analysis***

All analysis were carried out using IBM SPSS Statistics version 23. Non-parametric tests were used for com­paring ordinal scales and continuous variables (Mann-Whitney test) and for correlations (Spearman’s test). *2* test was used for crosstabs analyses and Fisher exact test if the number of cases was below 10. Student-*t* test was used for parametric comparison. A two-sided *P* value less than 0.05 were regarded significant. Means and standard deviations were used for continuous variables and medians and inter quartile range (IQR) for ordinal variables. No correction for multiple testing was applied. A logistic regression (SPSS/analyze/regression/binary logistic) was used for adjusting for possible confounders to the dependent variable GSRS-IBS score (dichotomous variable divided by median score). In the regression model age and body mass index were regarded as continues variables. HADS-D was categorized into two groups according to the accepted “cut-off” at ≥ 8 points, HADS-A was categorized into two groups according to the accepted “cut-off” at ≥ 9 points[18,19], PSQ index was categorized into two groups according the estimated moderate level of perceived stress (PSQ index > 0.34)[21] and the number of drugs was categorized into two groups by the median value. Each single drug used by more than ten patients with bipolar disorder was separately analyzed with age, body mass index, sex HADS-A and HADS-D.

**RESULTS**

***Patients with bipolar disorder in comparison to control subjects***

Patients with bipolar disorder had significant higher body mass index and scored significant higher on HADS scales in comparison to control subjects. Forty-eight (35%) of the bipolar patients versus 18 (13%) of the controls had either HADS-D scores ≥ 8 or HADS-A scores ≥ 9 (*P* < 0.001). Thirty-four percent (*n* = 46) of the patients with bipolar disorder had a PSQ index > 0.34 (estimated moderate or high perceived stress level). Total GSRS-IBS score was significant higher for patients with bipolar disorder than for controls. There were two symptom clusters that were significant higher among the patients; “the diarrhoea cluster” and “the satiety cluster” (Table 1). The patients with bipolar disorder tended to more often consulted primary care for a functional GI disorder than control subjects. Drug intake (number of drugs) was significant higher in patients with bipolar depression disorder compared to controls (median number 3 *vs* 1, *P* < 0.001). Drugs for affective disorders, drugs for insomnia, levothyrexine, antacids therapy and IBS medications were significant more common among patients with bipolar disorder whereas analgesic were more seldom used in compa­rison to control subjects.

***Association of affective symptoms and GI symptoms in bipolar disorder patients***

Bipolar patients with low HADS-D and HADS-A scores reported GI symptoms to the same extent as control subjects with low HADS-D and HADS-A scores despite a higher use of medications (Table 2). Except for sub scores for “constipation” and “reflux”, there were significant correlations between all GSRS and all HADS sub scores, and the bipolar patients with high HADS-A and/or HADS-D scored higher on GI symptom clusters (than patients with low HADS scores (Tables 2 and 3). There was a significant higher consulting rate in primary care for IBS in the patients with current high HADS-D in comparison to the patients with low HADS-D score (29% *vs* 8%, *P* = 0.008). Also control subjects with high HADS-A and/or HADS-D had higher GSRS scores than controls with low HADS scores [median scores of GSRS-IBS 12 (IQR 23) *vs* 6.5 (IQR 13), *P* = 0.021] as well as for sub scores for “bloating” (*P* = 0.005) and “diarrhoea” (*P* = 0.013).

***Logistic regression of factors that may influence GI symptoms***

Table 4 shows the characteristic of patients with high versus low GSRS-IBS score. Female sex, high scores on anxiety and depression, the use of benzodiazepines (“borderline significance”) and the use of drugs for insomnia was significant more common in patients with high GSRS-IBS score. A logistic regression was preformed to analyze potential confounders that influence the presence of GI symptoms in patients with bipolar disorder. In the logistic regression model only female sex and high HADS-D score was significantly associated to IBS symptoms (Table 5) in the patients with bipolar disorder.

Neither number of drugs (“cut off median number of drugs”) (Table 5) or any single drug adjusted for age, sex, body mass index and HADS score significantly influenced GI symptoms.

***Bipolar disorder type I vs type II***

The patients with bipolar disorder type Ⅰ were older than the patients with bipolar disorder type Ⅱ (mean 51.9 years *vs* 46.2 years, *P* = 0.025). There were no significant differences in GSRS-IBS scores, HADS scores or GI visits between the subtypes of bipolar disorder.

**DISCUSSION**

This present study, for the first time, aims to determine the extent in which affectivity is related to GI symptoms in a patient sample with an established bipolar disorder, a disorder characterized with fluctuating periods of hypomania/mania and depression. Our study shows that there is a strong association between symptoms of affectivity and GI symptoms in patients with bipolar disorder but also shows that patients with bipolar disorder with low scores on affectivity do not have more GI symptoms than control subjects. The latter is despite a more frequent use of medications with GI side-effects (*i.e.,* neuroleptics, SSRIs) in patients with bipolar disorder. Therefore, unexplained GI-symptoms in patients with bipolar disorder should be seriously considered to suffer from depression and receive adequate treatment. It is tempting to assume that this would reduce the number of unnecessary somatic examinations. We have previously shown that also patients with an established recurrent depression disorder report high scores on GI symptoms, but when in remission they do not differ from controls in reporting GI symptoms[6]. We believe that the present study and our previous study support that affectivity has an effect on the gut.

How the brain-gut axis is involved in the patho­physiology of anxiety/depression is not known. In the brain areas that process visceral afferents and areas involved in fear and anxiety are closely related. For example, functional imaging studies on patients with IBS have shown that balloon distension of the rectosigmoid colon increases activity in certain areas of the brain involved in the regulation of affective and sensory processes such as the amygdala, insula, cingulated and prefrontal cortex[23-26].

There is also evidence that gut symptoms and visceral hypersensitivity improve in patients with IBS treated with anti-depressants, hypnosis and cognitive-behavioural treatment[27-29]. One possible mechanism of these therapies could be an increase in prefrontal inhibition of the amygdale and anterior cingulated cortex[30].

Another factor that links affectivity and the gut is corticotrophin-releasing hormone (CRH). Anxiety, depression and stress are associated with increased activity of CRH[31]. CRH receptors are abundant in the amygdale as well in the gut and an exaggerated CRH response has been linked both to anxiety and depression[31-33] as well to gut physiology[34-37]. For example, injection of CRH results in an increased visceral hypersensitivity, exaggerated colonic motility and inhibition of upper gut motility[34-37]. In a clinical perspective a high CRH drive may result in simul­taneous occurrence of increased affectivity, visceral pain, diarrhoea, urgency and dyspepsia. CRH also up regulates the hypothalamic-pituitary-adrenal axis leading to hypercortisolism and activates locus cereuleus[31] leading to a shift of the autonomic nervous system towards an increased sympathetic tone with possible complex downstream effects on the gut physiology (including motility, sensitivity, secretion and the gut immune system)[30,38,39].

The issue of the brain-gut axis is complex and many other possible factors may also be involved. For example, the gut microbiotica and/or subtle inflammation in the bowel may play a role in the regulation of mood[40], indicating that in addition to a brain-gut axis there is also a gut-brain axis involved in the “link between affectivity and bowel symptoms.

In the logistic regression analysis in our study depressive symptoms and not anxiety symptoms and not perceived stress were related to GI symptoma­tology. This is a novel and important finding, which is contrary to that seen in studies on patients with IBS[18,41] and control subjects[42] in where anxiety correlates to an higher extent to reported GI symp­toms. Women and younger individuals score in general higher on HADS-anxiety[18] and perceived stress[21]. The majority of patients with IBS are women and younger, whereas the patients in the present study are older and involves relatively more men. These differences in age and gender distribution may partly explain the different impact of anxiety and depression on GI symptomatology in patients with IBS and patients with bipolar disorder. We suggest further studies that focus on the different aspects of affectivity and their impact on symptoms from the gut.

There are some limitations of our study. The GSRS and GSRS-IBS questionnaire is designed to be a sensitive tool for detecting symptoms typically of functional GI disorders[15,16]. However, the questions in the GSRS questionnaire only focus on symptoms the last week which increases the validity of the responses but at the same time disallows us from making a diagnosis according to the ROME criteria. GSRS is regarded by some authors to overestimate functional GI disorders in comparison to the ROME based questionnaires[43]. Two questions in the GSRS-IBS questionnaire issue the symptoms typically of postprandial dyspepsia (satiety and early satiety) and are inappropriate to be classed in the IBS-like symptom cluster. Because the questionnaire was valid with the “satiety” questions we have included the questions in the total GSRS-IBS[15].

The study design in the present study was mainly cross-sectional, which results in a lack of clear temporal relationship between depressive mood and GI symptoms. A prospective study design, analyzing GI symptoms in patients with affective disorder over time would better investigate this temporal relationship. Also, in studies comparing results from questionnaires there is some risk of reporting bias (reporting the same type of dignity on different scales). However, because of the fact that patients in remission (low HADS-D and HADS-A score) did not differ from controls in GI symptom score but the same patients tended to have more visits in primary care for functional GI complaints we argue that these data point toward a common pathophysiology between mood and gut symptoms in patients with bipolar disorder.

Female patients and patients with high HADS depression score reported significantly more GI symptoms, whereas patients with low HADS scores did not differ from control subjects. Unexplained GI-symptoms in bipolar patients should be seriously considered to suffer from depression and receive adequate treatment.

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**COMMENTS**

***Background***

Symptoms of anxiety and depression as well as increased stress-proneness are frequently occurring in patients with unexplained gastrointestinal (GI) symptoms, however the cause and effect relationship has not been clearly established

***Research frontiers***

There are many studies performed on patients with functional GI symptoms that investigate the prevalence and characteristics of symptoms of anxiety and depression. These patients often have longstanding and disabling gut symptoms with negative consequences on quality of life which in the long run may have an impact on mood. A different approach for studying how affective syndromes influence the bowel and brain-gut interactions is to set the starting point at the psychiatric patients. In the literature there are relatively few studies using this approach.

***Innovations and breakthroughs***

The present study supports a relationship between affectivity and gut symptoms. The finding that patients with bipolar disorder with low scores on affectivity do not have more GI symptoms than control subjects whereas patients with bipolar disorder with high scores on affectivity do have GI symptoms support the thesis that mood has an impact on gut function.

***Applications***

Unexplained GI-symptoms in bipolar patients should be seriously considered to suffer from depression and receive adequate treatment.

***Peer-review***

The idea of search is significantly studied throughout function bowel disorders, with all types and disorders. Results confirm what we expected, no changes from previous studies.

**REFERENCES**

1 **Palsson OS**, Whitehead WE. The growing case for hypnosis as adjunctive therapy for functional gastrointestinal disorders. *Gastroenterology* 2002; **123**: 2132-2135 [PMID: 12454867 DOI: 10.1053/gast.2002.32392]

2 **Koloski NA**, Jones M, Kalantar J, Weltman M, Zaguirre J, Talley NJ. The brain--gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study. *Gut* 2012; **61**: 1284-1290 [PMID: 22234979 DOI: 10.1136/gutjni.2011.300.474]

3 **Mayer EA**, Craske M, Naliboff BD. Depression, anxiety, and the gastrointestinal system. *J Clin Psychiatry* 2001; **62** Suppl 8: 28-36; discussion 37 [PMID: 12108819]

4 **Talley NJ**, Howell S, Poulton R. The irritable bowel syndrome and psychiatric disorders in the community: is there a link? *Am J Gastroenterol* 2001; **96**: 1072-1079 [PMID: 11316149 DOI: 10.1111/i1572-0241.2001.03741.x]

5 **Garakani A**, Win T, Virk S, Gupta S, Kaplan D, Masand PS. Comorbidity of irritable bowel syndrome in psychiatric patients: a review. *Am J Ther* 2003; **10**: 61-67 [PMID: 12522523 DOI: 00045391-200301000-00014]

6 **Karling P**, Danielsson A, Adolfsson R, Norrback KF. No difference in symptoms of irritable bowel syndrome between healthy subjects and patients with recurrent depression in remission. *Neurogastroenterol Motil* 2007; **19**: 896-904 [PMID: 17973640 DOI: 10.1111/j.1365-2982.2007.00967.x]

7 **Corruble E**, Guelfi JD. Pain complaints in depressed inpatients. *Psychopathology* 2000; **33**: 307-309 [PMID: 11060514]

8 **Gerber PD**, Barrett JE, Barrett JA, Oxman TE, Manheimer E, Smith R, Whiting RD. The relationship of presenting physical complaints to depressive symptoms in primary care patients. *J Gen Intern Med* 1992; **7**: 170-173 [PMID: 1487765]

9 **Cadoret RJ**, Widmer RB, North C. Depression in family practice: long-term prognosis and somatic complaints. *J Fam Pract* 1980; **10**: 625-629 [PMID: 7365435]

10 **Swanson SA**, Crow SJ, Le Grange D, Swendsen J, Merikangas KR. Prevalence and correlates of eating disorders in adolescents. Results from the national comorbidity survey replication adolescent supplement. *Arch Gen Psychiatry* 2011; **68**: 714-723 [PMID: 21383252 DOI: 10.1001/archgenpsychiatry.2011.12]

11 **Leboyer M**, Kupfer DJ. Bipolar disorder: new perspectives in health care and prevention. *J Clin Psychiatry* 2010; **71**: 1689-1695 [PMID: 21190640 DOI: 10.4088/JCP.10m06347yel]

12 **Bryant-Comstock L**, Stender M, Devercelli G. Health care utilization and costs among privately insured patients with bipolar I disorder. *Bipolar Disord* 2002; **4**: 398-405 [PMID: 12519100 DOI: 10.1034/j.1399-5618.2002.011.48x]

13 **Rush AJ**, Weissenburger JE. Melancholic symptom features and DSM-IV. *Am J Psychiatry* 1994; **151**: 489-498 [PMID: 8147445 DOI: 10.1176/aip.151.4.489]

14 **Herlitz A**, Nilsson LG, Bäckman L. Gender differences in episodic memory. *Mem Cognit* 1997; **25**: 801-811 [PMID: 9421566 DOI: 10.3578/BF03211324]

15 **Wiklund IK**, Fullerton S, Hawkey CJ, Jones RH, Longstreth GF, Mayer EA, Peacock RA, Wilson IK, Naesdal J. An irritable bowel syndrome-specific symptom questionnaire: development and validation. *Scand J Gastroenterol* 2003; **38**: 947-954 [PMID: 14531531 DOI: 10.1080/00365520310004209]

16 **Dimenäs E**, Glise H, Hallerbäck B, Hernqvist H, Svedlund J, Wiklund I. Quality of life in patients with upper gastrointestinal symptoms. An improved evaluation of treatment regimens? *Scand J Gastroenterol* 1993; **28**: 681-687 [PMID: 8210982 DOI: 10.3109/00365529309098272]

17 **Zigmond AS**, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361-370 [PMID: 6880820 DOI: 10.1111/j.1600-0447.1983.tb09716.x]

18 **Herrmann C**. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res* 1997; **42**: 17-41 [PMID: 9055211 DOI: 10.1016/S0022-3999(96)00216-4]

19 **Bjelland I**, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52**: 69-77 [PMID: 11832252 DOI: 10.1016/S0022(01)00296-3]

20 **Levenstein S**, Prantera C, Varvo V, Scribano ML, Berto E, Luzi C, Andreoli A. Development of the Perceived Stress Questionnaire: a new tool for psychosomatic research. *J Psychosom Res* 1993; **37**: 19-32 [PMID: 8421257 DOI: 10.1016/0022-3999(93)90120-5]

21 **Bergdahl J,** Bergdahl M. Perceived stress in adults: prevalence and association of depression, anxiety and medication in a Swedish population. *Stress and Health* 2002; **18**: 235-241 [DOI: 10.1002/smi.946]

22 **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]

23 **Naliboff BD**, Berman S, Chang L, Derbyshire SW, Suyenobu B, Vogt BA, Mandelkern M, Mayer EA. Sex-related differences in IBS patients: central processing of visceral stimuli. *Gastroenterology* 2003; **124**: 1738-1747 [PMID: 12806606 DOI: 10.1016/S0016-5085(03)00400-1]

24 **Wilder-Smith CH**, Schindler D, Lovblad K, Redmond SM, Nirkko A. Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. *Gut* 2004; **53**: 1595-1601 [PMID: 15479679 DOI: 10.1136/gut.2003.028514]

25 **Tillisch K**, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. *Gastroenterology* 2011; **140**: 91-100 [PMID: 20696168 DOI: 10.1053/j.gastro.2010.07.053]

26 **Larsson MB**, Tillisch K, Craig AD, Engström M, Labus J, Naliboff B, Lundberg P, Ström M, Mayer EA, Walter SA. Brain responses to visceral stimuli reflect visceral sensitivity thresholds in patients with irritable bowel syndrome. *Gastroenterology* 2012; **142**: 463-472.e3 [PMID: 22108191 DOI: 10.1053/j.gastro.2011.11.022]

27 **Guthrie E**, Barlow J, Fernandes L, Ratcliffe J, Read N, Thompson DG, Tomenson B, Creed F. Changes in tolerance to rectal distension correlate with changes in psychological state in patients with severe irritable bowel syndrome. *Psychosom Med* 2004; **66**: 578-582 [PMID: 15272106 DOI: 10.1097/01.psy.0000128899.22514.c0]

28 **Ford AC**, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Moayyedi P. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol* 2014; **109**: 1350-1365; quiz 1366 [PMID: 24935275 DOI: 10.1038/ajg.2014.148]

29 **Boyce PM**, Talley NJ, Balaam B, Koloski NA, Truman G. A randomized controlled trial of cognitive behavior therapy, relaxation training, and routine clinical care for the irritable bowel syndrome. *Am J Gastroenterol* 2003; **98**: 2209-2218 [PMID: 14572570 DOI: 10.1111/j.1572-0241.2003.07716.x]

30 **Keightley PC**, Koloski NA, Talley NJ. Pathways in gut-brain communication: evidence for distinct gut-to-brain and brain-to-gut syndromes. *Aust N Z J Psychiatry* 2015; **49**: 207-214 [PMID: 25710826 DOI: 10.1177/0004867415569801]

31 **Claes SJ**. Corticotropin-releasing hormone (CRH) in psychiatry: from stress to psychopathology. *Ann Med* 2004; **36**: 50-61 [PMID: 15000347 DOI: 10.1080/07853890310017044]

32 **Mayer EA**. The neurobiology of stress and gastrointestinal disease. *Gut* 2000; **47**: 861-869 [PMID: 11076888 DOI: 10.1136/gut.47.6.861]

33 **Schulkin J**, Morgan MA, Rosen JB. A neuroendocrine mechanism for sustaining fear. *Trends Neurosci* 2005; **28**: 629-635 [PMID: 16214230 DOI: 10.1016/j.tins.2005.09.009]

34 **Taché Y**, Martinez V, Million M, Wang L. Stress and the gastrointestinal tract III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors. *Am J Physiol Gastrointest Liver Physiol* 2001; **280**: G173-G177 [PMID: 11208537]

35 **Fukudo S**, Nomura T, Hongo M. Impact of corticotropin-releasing hormone on gastrointestinal motility and adrenocorticotropic hormone in normal controls and patients with irritable bowel syndrome. *Gut* 1998; **42**: 845-849 [PMID: 9691924 DOI: 10.1136/gut.42.6.845]

36 **Fukudo S**, Kanazawa M, Kano M, Sagami Y, Endo Y, Utsumi A, Nomura T, Hongo M. Exaggerated motility of the descending colon with repetitive distention of the sigmoid colon in patients with irritable bowel syndrome. *J Gastroenterol* 2002; **37** Suppl 14: 145-150 [PMID: 12572883 DOI: 10.1007/BF03326434]

37 **Saito-Nakaya K**, Hasegawa R, Nagura Y, Ito H, Fukudo S. Corticotropin-releasing hormone receptor 1 antagonist blocks colonic hypersensitivity induced by a combination of inflammation and repetitive colorectal distension. *Neurogastroenterol Motil* 2008; **20**: 1147-1156 [PMID: 18761632 DOI: 10.1111/j.1365-2982.2008.01151.x]

38 **Aggarwal A**, Cutts TF, Abell TL, Cardoso S, Familoni B, Bremer J, Karas J. Predominant symptoms in irritable bowel syndrome correlate with specific autonomic nervous system abnormalities. *Gastroenterology* 1994; **106**: 945-950 [PMID: 8143999]

39 **Messay B**, Lim A, Marsland AL. Current understanding of the bi-directional relationship of major depression with inflammation. *Biol Mood Anxiety Disord* 2012; **2**: 4 [PMID: 22738397 DOI: 10.1186/2045-5380-2-4]

40 **Zhou L**, Foster JA. Psychobiotics and the gut-brain axis: in the pursuit of happiness. *Neuropsychiatr Dis Treat* 2015; **11**: 715-723 [PMID: 25834446 DOI: 10.2147/NDT.S61997]

41 **Karling P**, Danielsson Å, Wikgren M, Söderström I, Del-Favero J, Adolfsson R, Norrback KF. The relationship between the val158met catechol-O-methyltransferase (COMT) polymorphism and irritable bowel syndrome. *PLoS One* 2011; **6**: e18035 [PMID: 21437260]

42 **Karling P**, Norrback KF, Adolfsson R, Danielsson A. Gastrointestinal symptoms are associated with hypothalamic-pituitary-adrenal axis suppression in healthy individuals. *Scand J Gastroenterol* 2007; **42**: 1294-1301 [PMID: 17852841 DOI: 10.1080/00365520701395945]

43 **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.1365-2036.2008.0375.x]

Footnotes

Institutional review board statement: The study was approved by the local committee for human ethics, Umeå University, Dnr 92-158, 01-095. 03-143, 03-484, 08-132M, 09-015M.

Clinical trial registration statement: The study was not registered at URL.

Informed consent statement: All patients gave informed consent prior to study enrolment.

Conflict-of-interest statement: No benefits in any form have been received or will be received from commercial party related directly or indirectely to the subject of this article.

Data sharing statement: Dataset available from the corres­ponding author at pontus.karling@umu.se.

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**Table 1 Basal characteristic in patients with bipolar disorder and control subjects representative of a general population**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Bipolar disorder** | **Controls** | ***P* value** |
| **(*n* = 136)** | **(*n* = 136)** |
| Mean age (SD) (yr) | 49.9 (14.1) | 51.0 (11.4) | 0.505 |
| Women | 61% (*n* = 83) | 60% (*n* = 81) | 0.804 |
| Mean body mass index (SD) (kg/m2) | 27.0 (5.50) | 25.41 (3.19) | 0.0051 |
| Median HADS scores (IQR): |  |  |  |
| HADS-anxiety | 5 (7) | 4 (5) | 0.0011 |
| HADS-depression | 3 (5) | 3 (3) | 0.0221 |
| PSQ index (IQR) | 0.27 (0.27) | NA |  |
| Median GSRS scores (IQR): |  |  |  |
| Abdominal pain | 1.00 (2.00) | 0.50 (1.50) | 0.076 |
| Bloating | 1.00 (1.67) | 0.50 (1.34) | 0.419 |
| Diarrhoea | 0.50 (1.50) | 0.25 (0.75) | 0.0021 |
| Constipation | 0 (2.00) | 0 (1.00) | 0.310 |
| Satiety | 0 (1.00) | 0 (0.50) | 0.0191 |
| Dyspepsia | 0 (1.00) | 0.33 (0.67) | 0.850 |
| Reflux | 0 (1.00) | 0 (0.50) | 0.376 |
| Total GSRS-IBS | 9.00 (17.00) | 7.00 (13.00) | 0.0201 |
| Consulters for: |  |  |  |
| Any functional GI disorder | 25% (*n* = 34) | 17% (*n* = 23) | 0.108 |
| IBS | 12% (*n* = 17) | 10% (*n* = 14) | 0.582 |

1Statistical significance. For each separate symptom cluster in the Gastrointestinal Symptom Rating Scale the total score was divided by the amount of items. HADS: Hospital Anxiety and Depression Scale; GSRS: Gastrointestinal Symptom Rating Scale; IBS: Irritable Bowel Syndrome; PSQ: Perceived Stress Questionnaire; IQR: Intra quartile range; NA: Not available.

**Table 2 Control subjects and patients with bipolar disorder with low scores on depression and low scores on anxiety score *vs* patients with high scores on depression and/or high scores on anxiety**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Bipolar patients with HADS-D ≥ 8 and/or HADS-A ≥ 9 (*n* = 48)** | **Bipolar patients with HADS-D < 8 and HADS-A < 9 (*n* = 88)** | **Controls with HADS-D < 8 and HADS-A < 9 (*n* = 118)** |
| Mean age (SD) (yr) | 46.7 (12.8) (*P* = 0.048)1 | 51.7 (14.4) | 51.5 (11.8) (*P* = 0.903) |
| Proportions of women | 58% (*n* = 28) (*P* = 0.634) | 62% (*n* = 55) | 59% (*n* = 70) (*P* = 0.644) |
| Mean Body mass index (kg/m2) (SD) | 27.2 (4.6) (*P* = 0.632) | 26.8 (5.97) | 25.6 (3.26) (*P* = 0.063) |
| Median HADS score (IQR) |  |  |  |
| HADS-anxiety | 10.5 (5.0) | 3.0 (4.0) | 3.0 (4.0) (*P* = 0.660) |
| HADS-depression | 9.0 (9.0) | 2.0 (3.0) | 2.0 (3.0) (*P* = 0.505) |
| PSQ index (IQR) | 0.47 (0.28) (*P* < 0.001)1 | 0.20 (0.17) | NA |
| Median GSRS score (IQR): |  |  |  |
| Abdominal pain | 1.50 (2.50) (*P* = 0.002)1 | 0.50 (1.50) | 0 (1.50) (*P* = 0.558) |
| Bloating | 1.67 (2.33) (*P* < 0.001)1 | 0.67 (1.33) | 0.67 (1.67) (*P* = 0.415) |
| Diarrhoea | 1.25 (2.25) (*P* < 0.001)1 | 0.50 (1.00) | 0.25 (0.75) (*P* = 0.107) |
| Constipation | 0 (2.00) (*P* = 0.380) | 0 (1.50) | 0 (1.00) (*P* = 0.453) |
| Satiety | 0.50 (2.00) (*P* = 0.003)1 | 0 (0.50) | 0 (0.50) (*P* = 0.513) |
| Dyspepsia | 0.67 (1.33) (*P* = 0.002)1 | 0 (0.67) | 0.33 (0.67) (*P* = 0.291) |
| Reflux | 0 (2.13) (*P* = 0.098) | 0 (0.88) | 0 (0.50) (*P* = 0.796) |
| Total GSRS-IBS | 15.0 (23.0) (*P* < 0.001)1 | 7.00 (12.0) | 6.50 (13.0) (*P* = 0.513) |
| Consulters: |  |  |  |
| For any functional GI disorder | 29% (*n* = 14) (*P* = 0.407) | 23% (*n* = 20) | 14% (*n* = 17) (*P* = 0.131) |
| IBS | 17% (*n* = 8) (*P* = 0.290) | 10% (*n* = 9) | 10% (*n* = 12) (*P* = 0.995) |
| Median number of drugs (IQR) | 3.0 (3.0) (*P* = 0.557) | 3.0 (3.0) | 1.0 (2.0) (*P* < 0.001)1 |

1Statistical significance. For each separate symptom cluster in the Gastrointestinal Symptom Rating Scale the total score was divided by the amount of items. HADS: Hospital Anxiety and Depression Scale; GSRS: Gastrointestinal Symptom Rating Scale; GI: Gastrointestinal; IBS: Irritable bowel syndrome; IQR: Intra quartile range; NA: Not available.

**Table 3 Hospital Anxiety Depression Scale scores and Perceived Stress Questionnaire index in correlation to different gastrointestinal symptom scores in patients with bipolar disorder (*n* = 136)**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HADS-Anxiety score.** | **HADS-Depression score.** | **PSQ index.** |
| **rs (*P* value)** | **rs (*P* value)** | **rs (*P* value)** |
| Abdominal pain | 0.295 (0.001)1 | 0.248 (0.004)1 | 0.261 (0.002)1 |
| Bloating | 0.304 (< 0.001)1 | 0.365 (< 0.001)1 | 0.376 (< 0.001)1 |
| Diarrhoea | 0.334 (< 0.001)1 | 0.225 (0.009)1 | 0.268 (0.002)1 |
| Constipation | 0.099 (0.254) | 0.028 (0.751) | 0.063 (0.473) |
| Satiety | 0.222 (0.010)1 | 0.253 (0.003)1 | 0.333 (< 0.001)1 |
| Dyspepsia | 0.293 (0.001)1 | 0.205 (0.017)1 | 0.287 (0.001)1 |
| Reflux | 0.245 (0.004)1 | 0.122 (0.160) | 0.235 (0.007)1 |
| Total GSRS-IBS score | 0.336 (< 0.001)1 | 0.328 (< 0.001)1 | 0.348 (< 0.001)1 |

1Statistical significance. Statistics: Spearman’s test. HADS: Hospital Anixiety and Depression Scale; GSRS: Gastrointestinal Symptoms Rating Scale; IBS: Irritable bowel syndrome; PSQ: Perceived Stress Questionnaire.

**Table 4 Comparison between patients with bipolar disorder who report high respective low scores on the Gastrointestinal Symptom Rating Scale for Irritable Bowel Syndrome**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **HIGH GSRS-IBS SCORE** | **LOW GSRS-IBS SCORE** | ***P* value** |
| **(> 9)** | **(≤ 9)** |
| **(*n* = 65)** | **(*n* = 71)** |
| Mean age (SD)(yr) | 49.7 (13.7) | 50.1 (14.5) | 0.571 |
| Women | 71% (*n* = 46) | 52% (*n* = 37) | 0.0261 |
| BMI (SD) | 27.2 (4.46) | 26.7 (6.32) | 0.45 |
| Median HADS scores (IQR) |  |  |  |
| Anxiety score (median) | 6.0 (9.0) | 4.0 (6.0) | 0.0011 |
| Depression score (median) | 4.0 (8.0) | 2.0 (4.0) | 0.0021 |
| PSQ index (IQR) | 0.32 (0.26) | 0.21 (0.23) | < 0.0011 |
| Consulters for: |  |  |  |
| Any functional GI disorder | 29% (*n* = 19) | 21% (*n* = 15) | 0.276 |
| IBS | 18% (*n* = 12) | 7% (*n* = 5) | 0.067 |
| Bipolar type Ⅰ | 46% (*n* = 40) | 54% (*n* = 48) | 0.460 |
| Bipolar type Ⅱ | 52% (*n* = 25) | 37% (*n* = 23) |
| Medications: |  |  |  |
| Lithium | 51% (*n* = 33) | 42% (*n* = 31) | 0.320 |
| Neuroleptics | 28% (*n* = 18) | 20% (*n* = 14) | 0.273 |
| Anti-epileptics | 31% (*n* = 20) | 34% (*n* = 24) | 0.706 |
| SSRI | 14% (*n* = 9) | 11% (*n* = 8) | 0.796 |
| SNRI | 9% (*n* = 6) | 6% (*n* = 4) | 0.519 |
| Benzodiazepines | 17% (*n* = 11) | 6% (*n* = 4) | 0.053 |
| Drugs for insomnia | 26% (*n* = 17) | 10% (*n* = 7) | 0.0141 |
| Drugs for IBS | 11% (*n* = 7) | 1% (*n* = 1) | 0.0281 |
| Antacids | 15% (*n* = 10) | 7% (*n* = 5) | 0.171 |
| Statines | 12% (*n* = 8) | 8% (*n* = 6) | 0.575 |
| Levothyroxine | 26% (*n* = 17) | 13% (*n* = 9) | 0.052 |
| ≥ 3 drugs | 64% (*n* = 41) | 54% (*n* = 38) | 0.214 |

1Statistical significance. HADS: Hospital anxiety and depression scale; GSRS-IBS: Gastrointestinal symptom rating scale- irritable bowel syndrome; PSQ: Perceived Stress Questionnaire; BMI: Body mass index; SSRI: Selective serotonin reuptake inhibitor; SNRI: Selective noradrenalin reuptake inhibitor; IQR: Intraquartile range.

**Table 5 Logistic regression analysis studying factors which may influence gastrointestinal symptoms in patients with bipolar disorder**

|  |  |  |
| --- | --- | --- |
|  | **Patients with bipolar disorder and GSRS-IBS > 9 *vs* patients with bipolar disorder and GSRS-IBS ≤ 9** | |
| **Unadjusted OR** | **Adjusted OR** |
| Age | 1.00 (0.97-1.03) | 1.01 (0.97-1.04) |
| Sex | 2.23 (1.09-4.52)1 | 2.37 (1.07-5.24)1 |
| (male reference) |
| Body mass index | 1.02 (0.95-1.09) | 1.01 (0.93-1.08) |
| HADS-Depression ≥ 8 | 5.54 (2.07-14.8)1 | 3.64 (1.07-12.4)1 |
| (< 8 reference) |
| HADS-Anxiety ≥ 9 | 2.89 (1.34-6.22)1 | 1.82 (0.64-5.22) |
| (< 9 reference) |
| PSQ index (≤ 0.34 reference) | 2.53 (1.21-5.30)1 | 1.30 (0.42-3.99) |
| Number of Drugs ≥ 3 | 1.55 (0.77-3.09) | 1.29 (0.59-2.80) |
| (< 3 reference) |

1Statistical significance. The dependent variable is high versus low score on the Gastrointestinal Symptom Rating Scale. The studied covariates were: Age (continues variable), Sex (dichotomous variable), Body mass index (continues variable), Hospital Anxiety and Depression scale score (dichotomous variable), Perceived Stress Questionnaire score (dichotomous variable) and Number of drugs (dichotomous variable with “cut off” being the median value). OR is presented with 95%CI. GSRS-IBS: Gastrointestinal symptom rating scale-irritable bowel syndrome; HADS: Hospital anxiety depression scale; PSQ: Perceived Stress Questionnaire.