

Case Control Study

Association between gastrointestinal symptoms and affectivity in patients with bipolar disorder

Pontus Karling, Martin Maripuu, Mikael Wikgren, Rolf Adolfsson, Karl-Fredrik Norrback

Pontus Karling, Department of Public Health and Clinical Medicine, Umeå University, S-90185 Umeå, Sweden

Martin Maripuu, Mikael Wikgren, Rolf Adolfsson, Karl-Fredrik Norrback, Department of Clinical Sciences, Division of Psychiatry, Umeå University, S-90185 Umeå, Sweden

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Correspondence to: Dr. Pontus Karling, Department of Public Health and Clinical Medicine, Umeå University, Universitetssjukhuset, S-90185 Umeå, Sweden. pontus.karling@umu.se
Telephone: +46-907-850000
Fax: +46-901-43986

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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.

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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 gastroesophageal 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). χ^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

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

	Bipolar disorder (<i>n</i> = 136)	Controls (<i>n</i> = 136)	<i>P</i> value
Mean age (SD) (yr)	49.9 (14.1)	51.0 (11.4)	0.505
Women	61% (<i>n</i> = 83)	60% (<i>n</i> = 81)	0.804
Mean body mass index (SD) (kg/m ²)	27.0 (5.50)	25.41 (3.19)	0.005 ¹
Median HADS scores (IQR):			
HADS-anxiety	5 (7)	4 (5)	0.001 ¹
HADS-depression	3 (5)	3 (3)	0.022 ¹
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)	0.002 ¹
Constipation	0 (2.00)	0 (1.00)	0.310
Satiety	0 (1.00)	0 (0.50)	0.019 ¹
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)	0.020 ¹
Consulters for:			
Any functional GI disorder	25% (<i>n</i> = 34)	17% (<i>n</i> = 23)	0.108
IBS	12% (<i>n</i> = 17)	10% (<i>n</i> = 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.

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

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/m ²) (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. rs (P value)	HADS-Depression score. rs (P value)	PSQ index. 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 Anxiety and Depression Scale; GSRS: Gastrointestinal Symptoms Rating Scale; IBS: Irritable bowel syndrome; PSQ: Perceived Stress Questionnaire.

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-

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 (> 9) ($n = 65$)	LOW GSRS-IBS SCORE (≤ 9) ($n = 71$)	P value
Mean age (SD)(yr)	49.7 (13.7)	50.1 (14.5)	0.571
Women	71% ($n = 46$)	52% ($n = 37$)	0.026 ¹
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)	0.001 ¹
Depression score (median)	4.0 (8.0)	2.0 (4.0)	0.002 ¹
PSQ index (IQR)	0.32 (0.26)	0.21 (0.23)	< 0.001 ¹
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% ($n = 7$)	0.014 ¹
Drugs for IBS	11% ($n = 7$)	1% ($n = 1$)	0.028 ¹
Antacids	15% ($n = 10$)	7% ($n = 5$)	0.171
Statins	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.

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, cingulate 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 amygdala and anterior cingulate

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 amygdala 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 microbiota 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

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 (male reference)	2.23 (1.09-4.52) ¹	2.37 (1.07-5.24) ¹
Body mass index	1.02 (0.95-1.09)	1.01 (0.93-1.08)
HADS- Depression ≥ 8 (< 8 reference)	5.54 (2.07-14.8) ¹	3.64 (1.07-12.4) ¹
HADS-Anxiety ≥ 9 (< 9 reference)	2.89 (1.34-6.22) ¹	1.82 (0.64-5.22)
PSQ index (≤ 0.34 reference)	2.53 (1.21-5.30) ¹	1.30 (0.42-3.99)
Number of Drugs ≥ 3 (< 3 reference)	1.55 (0.77-3.09)	1.29 (0.59-2.80)

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.

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.

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