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Psychosocial Characteristics and Pain Burden of Patients With Suspected Sphincter of Oddi Dysfunction in the EPISOD Multicenter Trial

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Abstract

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CONFLICT OF INTEREST

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Potential competing interests: None.

OBJECTIVES—Patients with several painful functional gastrointestinal disorders (FGIDs) are reported to have a high prevalence of psychosocial disturbance. These aspects have not been studied extensively in patients with suspected Sphincter of Oddi dysfunction (SOD).

METHODS—A total of 214 patients with post-cholecystectomy pain and suspected SOD were enrolled in seven US centers in a multicenter-randomized trial (Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction). Baseline assessments included pain descriptors and burden, structured psychosocial assessments of anxiety/depression, coping, trauma, and health-related quality of life. Patients with high levels of depression, suicidal ideation, or psychosis were excluded.

RESULTS—The study population (92 % female, mean age 38) reported anxiety (9 %), depression (8 %), past sexual trauma (18 %), and physical abuse (10 %). Of the total screened population (n = 1460), 3.9 % of the patients were excluded because of the presence of defined severe psychological problems. The mean medical outcomes study short-form-36 (SF-36) physical and mental composite scores were 38.70 (s.d. = 7.89) and 48.74 (s.d. = 9.60), respectively. Most subjects reported symptoms of other FGIDs. There were no correlations between the extent of the pain burden in the 3 months before enrollment and the baseline anxiety scores or victimization history. However, those with greater pain burden were significantly more depressed. There were no meaningful differences in the psychosocial parameters in subjects with or without irritable bowel, and those who had cholecystectomy for stones or functional gallbladder disease. Those declining randomization were comparable to those randomized.

CONCLUSIONS—Psychosocial comorbidity in SOD is high. However, it does not appear to differ significantly from that reported in surveys of age-and gender-matched general populations, and may be lower than reported with other FGIDs.

INTRODUCTION

Sphincter of Oddi dysfunction (SOD) encompasses a spectrum of disorders in which episodes of biliary/pancreatic-type pain are attributed to stenosis or spasm of the biliary and/or pancreatic sphincters. The diagnosis is most often considered in patients who have previously undergone cholecystectomy. About half of those will have some objective findings on laboratory studies or imaging (e.g., abnormal liver enzymes or a dilated bile duct), and are categorized by the Milwaukee classification as SOD types I and II (1,2). Patients who have similar symptoms, but who have no significant abnormalities demonstrated on standard imaging and laboratory tests, are categorized as suspected SOD III, with the supposition that episodes of pain are due to intermittent sphincter dysfunction. These patients are very difficult to evaluate and to manage effectively, not least because there are no objective markers of the condition (3).

Patients with burdensome pain are oft en referred to tertiary centers for evaluation and treatment. This usually involves endoscopic retrograde cholangio-pancreatography with Sphincter of Oddi manometry (SOM) (4), which is used to decide whether to perform sphincter ablation by endoscopic sphincterotomy of the biliary and/or pancreatic sphincters. As the results of these treatments are suboptimal, and carry significant hazards (e.g., occurrence of pancreatitis, bleeding, and perforation) (5), it is important to ascertain whether

additional factors, particularly psychosocial variables, co-occur and/or potentially modify pain symptoms in this patient population, and whether these factors affect treatment outcomes.

It is well recognized within the functional gastrointestinal disorder (FGID) population, in general, that patients with more severe and constant pain and psychosocial disturbance have poorer health status and treatment outcomes (6). Specifically, psychosocial factors affect gastrointestinal (GI) sensorimotor function and/or symptoms in FGID as predisposing, precipitating, or perpetuating factors (7). Numerous studies, examining FGID patient cohorts in various settings, mostly subspecialty clinics, reported high levels of comorbidity with psychiatric disorders, primarily mood and anxiety disorders, with most data obtained in patients diagnosed with irritable bowel syndrome (IBS) (6–11). Environmental stress in childhood and adulthood, specifically sexual and physical trauma, has been also linked with GI symptoms with high prevalence of abuse history among female patients in GI clinics and particularly in patients with IBS and other FGIDs (12–16). Sexual and/or physical abuse was reported in 40–50 % of patients with IBS and other FGIDs seen in referral GI clinics (15–16). Predictive analyses showed that psychosocial and behavioral features have an important role in determining the severity of painful functional bowel disorders, and a history of abuse is associated with greater pain reporting, greater psychological distress, poorer health status, and outcome regardless of the GI diagnosis (16). Maladaptive coping styles, such as “ catastrophizing,” feelings of helplessness, or inability to control symptoms, have also been implicated in the association between psychopathology and severity and outcome of FGID symptoms (17).

Surprisingly, despite these findings in other FGIDs, there are few studies focusing on suspected SOD cohorts. One small trial of 11 patients with suspected SOD and 10 control subjects examined visceral hyperalgesia (18). Although specifics were not provided, the authors noted that a sizeable minority of study patients scored in the 90th percentile for anxiety, depression, and somatization on the SCL-90-R inventory. Another study showed that both SOD patients and those with unexplained pancreatitis had high somatization scores, and abuse histories were common (19). A recently published abstract by Moffatt *et al.* (20) reported comparisons of psychometric profiles from a single center, measured by the SCL-90-R and the Whitely somatization index, between suspected SOD (n = 18 type 2 and n = 54 type 3) and non-SOD (n = 140) patients referred for endoscopic retrograde cholangio-pancreatography. They concluded that suspected SOD patients scored > 95th percentile for anxiety and depression levels as well as higher somatization and hostility than the non-SOD patients.

Because of the paucity of available prospective data, and to help shed light on the psychosocial underpinnings of this disabling condition, we undertook a prospective study of suspected type III SOD subjects in the EPISOD trial (Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction), an on-going, multicenter clinical trial designed to assess the efficacy and safety of sphincterotomy in patients diagnosed clinically with suspected SOD. The trial is funded by a grant from the National Institute of Diabetes, Digestion and Kidney Diseases (NCT00688662). This paper analyzes the baseline

characteristics of the EPISOD study population and assesses the prevalence of psychopathology and the relationship with baseline pain indices.

METHODS

Patients

The EPISOD study protocol has been reported in detail (21). It is a randomized, double-blind, sham-controlled trial conducted in patients with clinical characteristics suggestive of SOD. Patients referred to seven tertiary centers in the United States were initially "prescreened" to identify a cohort with the following characteristics: aged 18–65, significant pain-related disability after cholecystectomy, no pancreatic pathology or prior sphincter treatment, not taking narcotics daily, and apparently suitable for entry into a clinical trial. After consent, further criteria and questionnaires were applied. Pain characteristics had to be consistent with biliary SOD as defined by the ROME III criteria (4), modified to include patients with daily abdominal discomfort in addition to episodes of pain. Disability due to pain was measured by the recurrent abdominal pain intensity and disability (RAPID) instrument that was developed and validated specifically for this study, as other pain measures seemed inadequate to measure the burden of intermittent pains (22). It asks patients to report how much the three domains of work, house duties, and leisure were affected in the prior 90 days, with a maximum score of 270. For inclusion, patients had to report more than 11 days of disability due to pain (RAPID grade 3 or 4). Laboratory tests within 1 week and within 6 months of the baseline visit could not be more than two times the upper limit of normal for direct bilirubin, alkaline phosphatase, amylase, and lipase, and no more than three times the upper limit of normal for transaminases.

Patients receiving antidepressants for pain control must have been taking them for a minimum of 1 month before the baseline assessment, and patients with known depressive and/or anxiety disorders receiving psychopharmacological treatment must have been on a stable dose for at least 6 weeks. Baseline measures included the Mini International Neuropsychiatric Interview to assess presence of psychiatric disorders (23), anxiety/depression as measured by Hospital Anxiety and Depression Scale (HADS)-anxiety and depression subscales (HADS-A and HADS-D, respectively) (24) and the Beck depression inventory (BDI)-II (25), coping as measured by the Coping Skills Questionnaire-Catastrophizing Subscale (26), trauma as measured by the Trauma Questionnaire—Short Form (27) and health-related quality of life as measured by the SF- 36 (28). Patients were excluded if they had major psychiatric disorders (psychotic and bipolar disorders), current substance abuse, eating disorders, current severe depression (as defined by a BDI-II score of 22 or higher), or suicidal risk (assessed by BDI-II and Mini International Neuropsychiatric Interview questionnaires).

Study intervention

Eligible consenting subjects underwent endoscopic retrograde cholangio-pancreatography with pancreatic and biliary sphincter manometry. Subjects with successful pancreatic manometry, and without duct abnormalities such as pancreas divisum, were randomized using a 2:1 allocation to sphincterotomy or sham. Those allocated to the sphincterotomy

group who had elevated sphincter pressures were randomized a second time using a 1:1 ratio to either biliary or dual sphincterotomy. All subjects received a small (3–5 French guage diameter) temporary pancreatic stent to reduce the risk of post-procedure pancreatitis; none were given prophylactic anti-inflammatory medications. Subjects were observed in hospital overnight and returned to their referring physicians for standard clinical follow-up. Research coordinators at each site called the subjects at 1 week post procedure and monthly for 12 months. In addition, calls were made at 9 and 12 months by research staff at the central coordinating center to collect the primary outcome. The subjects, referring physicians and the callers were all blinded to the treatment allocation. Subjects dissatisfied with their progress were offered reassessment at the study site by an independent physician unaware of the treatment allocation.

Success was defined as patients having < 6 days of disability due to abdominal pain as measured using the RAPID instrument at months 9 and 12 post procedure, with no re-intervention during the follow-up period and no use of prescription analgesics for abdominal pain during months 10, 11, and 12.

Secondary outcomes included manometry results and their association with the primary outcome, success rates of subjects receiving biliary sphincterotomy as compared with dual sphincterotomy, the effect of prespecified potential prognostic factors, quality of life, and resource utilization.

Local institutional review board approval was obtained at all participating sites and written informed consent was obtained from the patients before study enrollment.

Patients who were otherwise eligible but who declined randomization were invited to participate in an observational study (EPISOD 2) in which sphincterotomy was performed based on the results of manometry.

Statistical analysis

SAS soft ware version 9 (SAS Institute, Cary, NC) was utilized to perform statistical analyses. Baseline variables were described using counts and percentages for categorical data or means and s.d. (medians and interquartile ranges) for continuous normal (skewed) data. Associations between disability and psychosocial measures as well as pain intensity and psychosocial measures were assessed using Pearson’s and Spearman’s correlations and multivariable linear and quantile regression. Quantile regression, similar to ordinary least squares regression, however, oft en utilized for non-normally distributed data, models the relationship between covariates and the conditional quantiles of the outcome variable (29). All tests were conducted using a two-sided significance level of < 0.05.

RESULTS

A total of 1,460 patients were prescreened for eligibility. Of these, 1,172 failed for a variety of reasons, the most common being “daily use of prescription analgesics” (n = 200), “liver function tests outside the allowable range” (n = 191), and “pain not severe enough to justify endoscopic retrograde cholangio-pancreatography” (n = 156). Twenty-nine (2.5 %) patients

were not considered further because of presence of obvious significant psychiatric disorders. Two hundred and eighty-eight patients consented to the study. Twenty-eight (10 %) of those were excluded for protocol-specific psychological exclusionary criteria. A total of 214 patients were randomized between July 2008 and March 2012. Seventy-two patients were enrolled into EPISOD 2, the naturalistic follow-up study.

The overall mean age of the EPISOD participants was 38 years. Most were females (92 %), non-Hispanic (92.5 %), and fully or part-time employed (73 %). Cholecystectomy had been performed on average 4 years before study enrollment. At cholecystectomy, 47 % were known to have gallstones; the remainder were shown or assumed to have had a functional gallbladder problem. Symptoms characteristic of IBS (as defined by Rome III) were present in 34 %. The median RAPID disability score in the 90 days before randomization was 74 (range: 11–270) and the average intensity of pain episodes (on a 10-point scale) was 7 (s.d. = 1.88). Fifty-five (26%) patients were taking narcotic analgesics for abdominal pain on an average of 33 days in the 3 months before enrollment.

Table 1 presents pain-related and psychosocial assessment data and their breakdown by quartiles of the RAPID scores. Eighty-four (39 %) patients received antidepressants and/or anxiolytics. Nine percent of the patients met criteria for an anxiety disorder (panic disorder and/or agoraphobia at 2.3 % and generalized anxiety disorder at 6.5 %) at baseline and 8 % had current depression (major depressive episode or dysthymia). Baseline median anxiety and depression scores were BDI-II of 7 (scale total score range: 0–26), HADS-D of 3 (scale total score range: 0–16) and HADS-A of 4 (total score range: 0–16). Median Coping Skills Questionnaire-Catastrophizing Subscale score was 6 (total score range: 0–32). Eighteen percent of patients reported past sexual trauma including inappropriate touching: < 13 years of age: 13 % touching; 3 % rape; 13 + years of age: 6 % touching; 4 % rape; 10 % reported physical abuse. The mean physical and mental composite scores on the medical outcomes study short-form 36 (SF-36) were 2 s.d. below the normal for physical component at 38.70 (s.d. = 7.89) and near-normal on the mental component at 48.74 (s.d. = 9.60).

Although frequency of pain episodes, SF-36 pain domain score, and use of antidepressants each worsen with increasing quartiles of the disability score, other measures such as pain intensity and daily abdominal discomfort did not show this pattern with disability score (Table 1). There was poor correlation between psychosocial measures and baseline pain-related disability for all psychosocial measures ($r < 0.50$). It is noteworthy that patients with higher RAPID scores had worse SF-36 mental composite scores and were more depressed, but they were not more anxious (Figure 1). Further, subjects with current diagnosis of depression or dysthymia as assessed by the Mini International Neuropsychiatric Interview had significantly higher median RAPID scores than those without the diagnosis (Figure 1: 120 days vs. 70 days; $P = 0.005$).

Table 2 illustrates the psychosocial and pain disability data in EPISOD patients with and without concomitant symptoms of IBS (by Rome III criteria), and the patients in EPISOD 2. There were significant higher depression scores in IBS patients when measured by BDI, but not HADS-D. There was no difference in psychosocial data in subjects with and without daily abdominal discomfort, and those with and without gallstones at cholecystectomy.

There were no significant differences between the randomized patients (EPISOD) and those treated by standard of care (EPISOD 2).

DISCUSSION

This is the largest reported data set of demographic, clinical, and psychosocial characteristics of patients with suspected SOD, with rigorous prospective collection. The important and surprising overall finding was the relatively low level of depression and anxiety despite high levels of disability due to pain. In fact, comparisons with age- and gender-adjusted US population norms indicated no statistically significant difference on SF-36 mental functioning ($P = 0.52$), although physical functioning score was significantly worse than the population norm ($P < 0.0001$). Eight percent of EPISOD patients met criteria for current depressive disorder and 9 % had a diagnosis of an anxiety disorder. These rates of anxiety and depressive disorders are lower than those reported in the many studies of patients with FGIDs, and even those derived from the general population. For example, in a landmark epidemiological study evaluating lifetime and current (12 month) prevalence of psychiatric disorders in an adult US population ($n = 8,089$), Kessler *et al.* (30) found that ~ 13% of female responders had a current diagnosis of major depression and over 22 % had an anxiety disorder. These prevalence rates are, by and large, consistent across other epidemiological studies (31). Similarly, severity of mood and anxiety symptoms in the EPISOD patients, as measured by HADS and BDI-II scales, was surprisingly comparable to those reported in normal populations (with population norm reports for mean HADS-A and HADS D scores of 5 and 4, respectively, and BDI-II score of 14 among female subjects) (32,33).

The extensive literature on other FGIDs have demonstrated prevalence rates of 50 % and higher for mood and anxiety disorders in subjects seen in clinical settings with IBS and other FGIDs (6–11). It should be noted that published studies vary greatly in their methodology and diagnostic assessment instruments; some utilized validated diagnostic instruments that employ strict diagnostic criteria, whereas others used self-report questionnaires, potentially explaining differences in results. Therefore, to help further understand the EPISOD population, we examined scores on patient-rated HADS-A and HADS-D using cutoff scores of ≤8, which is found to have the optimal sensitivity and specificity for potential “caseness” for depression and anxiety disorders (24,34). Twelve and 17 % of EPISOD patients met the above cutoff criteria on HADS-D and HADS-A, respectively. Although these rates are higher than depression and anxiety disorders rates based on the Mini International Neuropsychiatric Interview for Diagnostic and Statistical Manual of Mental Disorders-IV psychiatric disorders, a recent trial of 268 IBS subjects by Thijssen *et al.* (9) reported that 30 and 22 % of IBS subjects met HADS cutoff criteria for anxiety and depression, respectively, again indicating higher levels of mood and anxiety disturbance in IBS population.

As stated earlier, history of traumatization has been oft en associated with FGIDs, with numerous studies indicating high prevalence rates of sexual and physical trauma in these patients. In a population survey (12) of 919 responders, Talley *et al.* (13) reported a significant association between IBS and history of abuse. In a later study of GI outpatients, Talley *et al.* (13) found that 22 % of those with physician-based diagnosis of FGID had

some form of abuse vs. 16 % of those with structural disease. A study of an Italian sample of GI outpatients reported that 32 % of those with FGIDs had experienced sexual or physical abuse (14). Irwin *et al.* (15) reported 44% of abuse in 50 consecutive patients with IBS. Similarly, Drossman *et al.* (16) also reported 44 % sexual or physical abuse history in 206 GI clinic subjects. FGID patients were more likely than those with structural diagnoses to report rape or frequent physical abuse (16). In contrast, 24 % of EPISOD patients reported a history of sexual or physical abuse, with 18 % reporting some type of sexual abuse and 10 % physical abuse. These study results should be viewed in the context of the comparably high rates of abuse reported in representative samples of women in the United States (35–37).

Surprisingly, the presence of comorbid IBS did not have a significant effect on any of the psychosocial variables in EPISOD patients except somewhat higher endorsement of depressive symptoms and catastrophizing in the comorbid group, although these scores are lower than those observed by Drossman, in a sample of 431 well-defined IBS subjects with mean BDI-II score of 10.47 and Coping Skills Questionnaire-Catastrophizing Subscale of 10.02 in that cohort (D. Drossman, personal communication). Also, we found no difference in the measured characteristics of patients who had their cholecystectomies for organic pathology (gallstones) when compared with those done for demonstrated or assumed functional gall bladder disease.

Overall, the correlation between psychosocial measures and baseline pain intensity and pain disability was low for all psychosocial measures. However, we found that patients with more pain-related disability, as measured by RAPID scores, were significantly more depressed. This pattern was not seen when assessing anxiety.

It could be argued that patients with suspected SOD may differ from those with chronic functional GI disorders because of the episodic nature of their pain. Patients with intermittent pain presumably have pain that is most related to peripheral afferent excitation compared with patients with chronic functional GI disorders, or chronic pain in general, who have greater contributions of central sensitization and central nervous system disinhibition of pain regulatory pathways. The latter is strongly associated with high psychosocial disturbance (38,39). However, half of EPISOD patients did have some daily abdominal discomfort, and their levels of psychosocial disturbance were no different from the rest.

One may question whether these surprising results are generalizable, or only because of selection bias. It could be argued that patients who obtain referral to tertiary centers and agree to participate in a randomized, sham-controlled trial might not be representative of the whole SOD population. However, the baseline psychosocial characteristics of the 72 patients concurrently enrolled in the EPISOD 2 observational study were no different. An important argument against the idea that the data suffer from selection bias is that research studies in patients with IBS suggest that those who seek treatment are actually the more psychologically disturbed (11). As in many trials, site investigators were allowed to exclude potential patients at prescreening if they appeared to be unsuitable for a clinical trial, for any reason, including psychological disturbance. However, that reason for exclusion was noted in only 2.5 % of the total patients prescreened. Competitive enrollment into a sham-controlled trial rendered overuse of this exclusion unlikely. After consent, a further 28

patients were excluded for more defined and severe psychological problems. Two hundred potential subjects were excluded because they were taking daily narcotics (making assessment of treatment outcomes difficult) but only eight of these also failed study psychological entry criteria.

The EPISOD baseline data show that the psychosocial disability in patients with severe symptoms from suspected SOD may not be different than the general population, keeping in mind that the known rates of psychological issues and trauma history in age- and gender-matched populations are high. This may have significant implications for clinical practice, and we look forward to seeing how psychological comorbidity influences the clinical response to sphincterotomy or sham treatment in this population.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Sphincter of Oddi dysfunction (SOD) is currently considered to be one of the functional gastrointestinal disorders (FGIDs).
- Patients with FGIDs are believed to have significant psycho logical problems, including history of trauma. These aspects have not been studied extensively in patients with suspected SOD.

WHAT IS NEW HERE

- We report the demographics, pain burden, clinical, and psychological characteristics of a large cohort of patients with suspected SOD entering a randomized sham-controlled treatment study.
- The main finding is that these patients appear to be less psychologically distressed than reported from other FGID cohorts, indeed consistent with data from random population surveys.

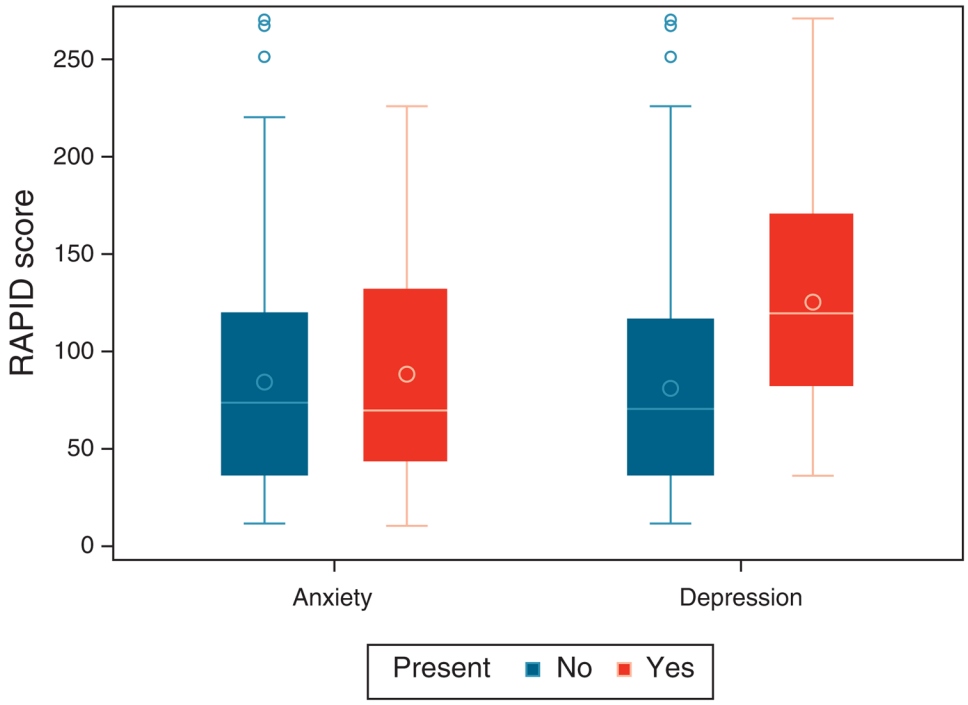

Figure 1.

RAPID scores by presence of Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV depressive and anxiety disorders. *P* value of Wilcoxon rank-sum test: anxiety = 0.79; depression = 0.005. RAPID, recurrent abdominal pain intensity and disability.

Table 1

Baseline psychosocial and pain characteristics by RAPID score quartiles

	Total sample	RAPID score (0–270)				Significance[a]
	N=214	Q1 (11–37) *N*=53	Q2 (38–73) *N*=54	Q3 (74–118) *N*=52	Q4 (120–270) *N*=55	*P* value
Gender (female)	92%	96%	94%	85%	93%	0.23
Days of pain episodes in past 90 days (mean s.d.)	69.05 (26.69)	56.15 (33.33)	68.98 (25.68)	73.23 (22.36)	77.58 (19.15)	**0.001**
Pain intensity (0–10) in past 90 days, mean (s.d.)	6.73 (1.88)	7.00 (2.08)	6.65 (1.76)	6.19 (1.82)	7.07 (1.78)	0.97
Pain burden (frequency×intensity product) in past 90 days, mean (s.d)	450.49 (205.41)	375.32 (250.86)	444.04 (182.94)	441.77 (176.17)	537.51 (174.04)	**0.0001**
Subjects with daily abdominal discomfort in past 30 days (%)	51%	58.5%	37%	58%	53%	0.93
SF-36 pain scale (mean s.d.)	34.96 (16.50)	44.11 (15.32)	36.24 (14.06)	32.40 (14.03)	27.29 (17.85)	< **0.0001**
Psychosocial variables						
DSM-IV depressive disorders (current) (%)	8%	2%	6%	8%	16%	**0.005**
DSM-IV anxiety disorders (current) (%)	9%	8%	11%	8%	9%	0.94
HADS-anxiety (0–21)	4.60 (3.50)	4.25 (3.44)	4.65 (3.43)	4.81 (3.44)	4.69 (3.74)	0.49
HADS-depression (0–21)	3.45 (3.10)	2.09 (2.26)	3.13 (2.58)	4.02 (3.70)	4.55 (3.17)	< **0.0001**
BDI-II (0–63)	7.75 (5.39)	5.47 (4.79)	6.61 (4.33)	8.87 (5.44)	10.02 (5.79)	< **0.0001**
CSQ-CAT sum score (0–36) (coping/catastrophizing)	7.58 (6.68)	6.92 (6.02)	7.74 (7.18)	8.39 (6.73)	7.31 (6.84)	0.80
SF-36 physical	38.70 (7.89)	42.88 (6.89)	40.53 (6.66)	37.00 (7.66)	34.48 (7.69)	< **0.0001**
SF-36 mental	48.74 (9.60)	51.82 (6.94)	50.28 (8.95)	46.80 (8.79)	46.09 (11.94)	**0.003**
Physical and/or sexual abuse history (%)	24%	24.5%	20%	29%	22%	1.00
Narcotics use (%)	26%	25%	26%	27%	27%	0.95
Antidepressant/anxiolytic use (%)	39%	38%	35%	35%	49%	0.33

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BDI-II, Beck depression inventory-II; CSQ-CAT, Coping Skills Questionnaire-Catastrophizing Subscale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; HADS, Hospital Anxiety and Depression Scale; RAPID, recurrent abdominal pain intensity and disability; SF-36, medical outcomes study short-form 36.

[a]Indicates overall statistical significance for comparisons across quartiles; hypothesis test was a test for trend in ordered alternatives, Jonckheere trend test was for continuous variables, and Cochrane–Armitage was for categorical variables.

Bold entries are those numbers that are statistically significant ($P \leq 0.05$).

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Table 2

EPISOD baseline psychosocial characteristics by IBS status, and EPISOD 2

Cohorts	**EPISOD without IBS (*N*=141)**	**EPISOD with IBS (*N*=73)**	**EPISOD2 (*N*=72)**
Gender (% female)	93	90	86
Age (mean s.d.)	38.45 (11.21)	38.32 (10.62)	39.86 (12.65)
Psychosocial variables (%)			
DSM-IV depressive disorders (current)	8.5	7	7
DSM-IV anxiety disorders (current)	8.5	10	8
Generalized anxiety disorder	6	8	4
Panic disorder	0	1	3
Agoraphobia	3	0	3
Social anxiety disorder	0	0	0
Posttraumatic stress disorder	0	0	0
Obsessive compulsive disorder	0	0	1
Positive physical and/or sexual abuse history	24	23	19
Physical abuse	9	12	6
Sexual abuse	19	15	15
Mean (s.d.)			
HADS-anxiety	4.31 (3.31)	5.15 (3.79)	4.32 (3.12)
HADS-depression	3.23 (2.95)	3.89 (3.34)	3.51 (3.25)
BDI-II	7.11 (4.97)	9.00 (5.98)	8.47 (5.47)
CSQ-CAT score (coping/catastrophizing)	7.10 (6.56)	8.49 (6.87)	8.07 (6.88)
SF-36 physical	39.21 (7.68)	37.72 (8.24)	38.49 (8.87)
SF-36 mental	49.13 (9.47)	47.99 (9.85)	48.11 (10.15)
Baseline RAPID (median (min–max))	80.00 (11–270)	64.00 (12–270)	49.50 (11–260)

BDI-II, Beck depression inventory-II; CSQ-CAT, Coping Skills Questionnaire-Catastrophizing Subscale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; EPISOD, Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction; HADS, Hospital Anxiety and Depression Scale; IBS, irritable bowel syndrome; RAPID, recurrent abdominal pain intensity and disability; SF-36, medical outcomes study short-form 36.