Quality of life, anxiety, depression in patients with inflammatory bowel disease

From screening to the effect of a cognitive behavioural intervention

Bennebroek Evertsz', F.

CHAPTER 8

EFFECTIVENESS OF COGNITIVE BEHAVIOURAL THERAPY ON QUALITY OF LIFE, ANXIETY AND DEPRESSION AMONG PATIENTS WITH INFLAMMATORY BOWEL DISEASE: A MULTICENTRE RANDOMISED CONTROLLED TRIAL

F. Bennebroek Evertsz', M.A.G. Sprangers, K. Sitnikova, P.C.F. Stokkers, C.Y. Ponsioen, J.F.W.M. Bartelsman, A.A. van Bodegraven, S. Fischer, A.C.T.M. Depla, R.C. Mallant, R. Sanderman, H. Burger, C.L.H. Bockting.

Journal of Consulting & Clinical Psychology 2017 Sep; 85(9): 918-925.

ABSTRACT

Objective: Inflammatory bowel disease (IBD) is characterized by a low level of quality of life (QoL) and a high prevalence of anxiety and depression especially in patients with poor QoL. We examined the effect of IBD-specific Cognitive Behavioural Therapy (CBT) on QoL, anxiety, depression and disease activity in IBD-patients with poor mental QoL.
Method: This study is a parallel-group multicentre randomised controlled trial (RCT). 118 IBD-patients with a low level of QoL (score≤23 on the mental-health-subscale of the SF-36) were included out of two academic medical centres (AMC, VUmc) and two peripheral medical centers (Flevo Hospital,Slotervaart) in the Netherlands. Patients were randomised to an experimental-group receiving CBT (n=59) versus a waitlist-control-group (n=59) receiving standard medical care for 3.5 months, followed by CBT. Both groups completed baseline and 3.5 month follow-up assessments. The primary outcome was a self-report questionnaire and disease-specific-QoL (IBDQ). Patients were aware of assignment to randomisation. Secondary outcomes were depression (HADS-D; CES-D), anxiety (HADS-A), generic QoL (SF-36) and disease-activity (C-reactive protein (CRP), platelets, leukocytes, haemoglobin and Physician's Global Assessment(PGA)).
Results: Data were analysed both on intention-to-treat as well as on per protocol analysis (completed ≥5 sessions). CBT had a positive effect on disease-specific-QoL (Cohen's d=0.64 for IBDQ total-score), depression (Cohen's d=0.48 for HADS-D and 0.78 for CES-D), anxiety (Cohen's d=0.58 for HADS-A) and generic QoL (Cohen's d=1.08 for MCS of the SF-36); all $p<0.01$.
Conclusions: IBD-specific CBT is effective in improving QoL and in decreasing anxiety and depression in IBD-patients with poor QoL. Clinicians should incorporate screening on poor mental QoL and consider offering CBT.

What is the public health significance of this article?
Given that a substantial proportion of people with chronic somatic disorders have a high prevalence of psychiatric disorders, it is of relevance to examine whether psychological interventions are effective in this comorbid group. In a specific chronic somatic disorder, inflammatory bowel disease (IBD), 'IBD-specific CBT' has a promising effect on QoL, anxiety and depressive symptoms.

INTRODUCTION

Inflammatory Bowel Disease (IBD) is a debilitating and chronic inflammatory condition of the intestinal tract ranging from the mouth to the anus (Crohn's Disease; CD), whereas Ulcerative Colitis (UC) is restricted to inflammation of the colon. Its incidence is steadily increasing worldwide. [1] As the inflammation in CD is transmural, it may lead to abscess and fistula formation(penetrating phenotype) or strictures of the intestinal lumen (fibrostenoticphenotype). These complications are very rare in UC. UC is more often complicated by development of a toxic megacolon. A toxic megacolon is a life-threatening condition requiring hospital admission and sometimes surgical removal of the colon. To date, there is no cure for IBD. Patients usually require life-long medical treatment and surgery at some point in time. [2] Multiple factors (i.e. genetics, microbiota, environment and immune response) contribute to the aetiology of IBD. [3] Individuals with IBD report poorer quality of life (QoL) [4] and more anxiety and depressive symptoms than controls. [5,6] As in other somatic diseases [7] poor QoL and co-morbid depression and anxiety adversely affect illness course. For IBD, this means higher relapse rates and more disease-activity. [5] Between 60% and 80% of IBD patients suffer from anxiety and depressive disorders during exacerbation and 29% - 35% during illness remission . [8]

Cognitive behavioural therapy (CBT) is the most investigated and effective treatment in reducing anxiety and depressive symptoms in patients with chronic illnesses. [9,10] Nevertheless, reviews [11,12,13] reported mixed results on the effectiveness of psychological interventions on anxiety, depression, QoL and disease-activity in IBD-patients and most studies suffered major methodological shortcomings, such as lack of a control group or insufficient sample size (the range of N is 4-72). Only seven studies [14,15,16,17,18,19,20] covered aspects of CBT-interventions in adults with IBD, two of which [14,15] did not assess QoL, depression and anxiety. These studies did not preselect IBD-patients with high functional impairment. The current study will address these shortcomings by conducting a randomised controlled trial (RCT) amongst a larger sample of IBD-patients with mental health disorders, i.e. poor mental QoL. [21] We specifically focus on this high-risk group as poor QoL is associated with the presence of psychiatric disorders and functional impairment. [6]

Our aim is to examine the effectiveness of IBD-specific CBT on QoL, anxiety, depression and, secondary disease-activity in a multicentre RCT, comparing an experimental group receiving CBT to a waitlist control group.[22] We expect a greater improvement in health- related-QoL and a larger reduction in the depressive- and anxiety symptoms of patients who receive CBT than in the waitlist control group. Finally, the effect of CBT on disease-activity will be examined.

METHODS

Study design and participants

Eligible patients had to meet the following inclusion criteria: 1) a diagnosis of Crohn's disease (CD) or ulcerative colitis (UC); 2) age above 18 years; 3) score of ≤ 23 on the mental health subscale of the MOS Short Form 36(SF-36) [23]; 4) physically and mentally able to attend eight weekly sessions; 5) sufficient command of Dutch. Exclusion criteria were: 1) current psychotherapy; 2) severe other psychiatric disorders (i.e. substance abuse, bipolar disorder or psychosis) as assessed with the Structural Clinical Interview for DSM IV Axis-1 Disorders (SCID-I). [24] Patients were randomized to receive standard medical care (waitlist control group) or CBT in addition to standard medical care. Patients in the waitlist control group were treated with CBT 3.5 months after study enrollment.

Consecutive patients were screened for eligibility and enrolled by independent gastroenterologists from the four participating medical centres (Academic Medical Centre (AMC), Flevo Hospital, Slotervaart Hospital, VU University Medical Centre (VUmc)). IBD was diagnosed based on the usual clinical criteria, comprising clinical history, physical examination, laboratory findings, negative stool cultures, radiological imaging and endoscopic and histological examinations as assessed by IBD-experts, at least 3-6 months before entry in the study. The study was explained orally and subsequently an informed consent form was handed over. One week later the researcher called to give patients further information about the study and appointments were made with those who signed the form. A trained psychologist then carried out a telephone-version of the validated SCID-I [24]; in order to determine inclusion/ exclusion criteria.

The study-protocol was approved by the Medical Ethical Committee of the AMC and confirmed by local institutional ethics review committees at the participating medical centres. The trial was registered at the national trial register before start of the study NTR (TC=1869) http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1869 [25]

Randomisation and masking

After completing the first baseline-assessment, an independent collaborator randomly allocated patients using the TENALEA Clinical Trial Data Management System software. Randomisation was performed on a 1:1 ratio using non-deterministic minimization to enhance balance between the groups on important prognostic factors (gender, disease-type (CD and UC) and type of medical centre (peripheral versus academic)). [26] Our algorithm added a random, non-deterministic component by assigning a probability of 0.83 of being allocated to the preferred arm.

Patients were informed on assignment after completing the baseline-assessments online. Due to the nature of our trial patients, neither CBT therapists nor researchers could be kept blind to treatment assignment. Data were imported and analysed after

all patients had completed the trial. If patients did not respond within two weeks, an automatic reminder was sent by e-mail.

Procedures

The individual IBD-specific CBT involved eight, one-hour-long weekly sessions. A treatment manual was based on the CBT model [27] and was used to enhance treatment integrity (available on request from the first author. All patients received writing-assignments, cognitive interventions focused on specific illness beliefs (for example 'my illness has major consequences on my life') and dysfunctional attitudes (for example 'I have to be perfect to be happy') and a relapse-prevention plan. [22] There were two optional additional modules, depending on the specificpsychiatric disorder: 1) behavioural activation andan exposure-based response preventionmodule (respectively for depressive and anxiety disorders) and 2) imagination and rescripting (for PTSD).

Eighteen clinical psychologists specialized in CBT were assigned to perform the intervention in this trial. Each therapist received 16 hours of additional training on IBD-specific CBT and regular group-supervision during the study period (between 11 and 17 hours). All CBT- sessions were audio recorded. Independent raters conducted integrity checks on at least two treatments per therapist.

Standard medical care involved consultation with medical specialist every three months if immune suppression was used and once a year for patients not receiving immune suppression. There were no restrictions on consulting medical specialists, general practitioners or using medication.

Outcomes

The experimental group started CBT immediately and completed follow-up measures one month after its completion. After the baseline-assessment, those in the waitlist control group waited 3.5 months to start CBT and completed a follow-up assessment one month after its completion. All assessments were based on online self-report questionnaires.

The primary outcome was the total-score on the Inflammatory Bowel Disease Questionnaire (IBDQ) at the 3.5 months' follow-up, an illness-specific health-related-QoL score, consisting of 32 items assessing four domains; bowel symptoms, systemic symptoms, emotional and social functioning. [28]

The secondary outcomes were depression and anxiety, which were assessed using the Hospital Anxiety and Depression Scale (HADS), a measure specifically designed for patients with somatic illness. A score ≥8 on either subscale indicates a possible psychiatric-, anxiety- and/or depressive disorder and a score ≥11 indicates a probable psychiatric disorder in the same category. [29] The Centre for Epidemiologic Studies - Depression Scale (CES-D) measuring depressive symptomatology in the general population was additionally used to examine the difference between these two questionnaires. [30]

Generic health-status was assessed with the SF-36.[23] The 36 items can be aggregated into a Physical-Component-Summary (PCS) score and a Mental-Component-Summary (MCS) score. The scores range from 0-100, with higher scores indicating better physical or mental health. All questionnaires have been widely validated before.[28,29,30,23]

Sociodemographic variables included patient-reported gender, age, marital-status, level of education, employment-status and hospital-type. Clinical data including disease-type, disease-duration in years, sick-leave, number of operations, presence of a stoma, use of medication with depression as side-effect, use of antidepressants and family-members with IBD (Table 1) were gathered by the treating gastroenterologist.

The biological markers of disease-activity were collected from the electronic-patient-database within a time frame of 4 weeks prior to and 4 weeks after the baseline- or follow-up assessment. These are C-reactive protein (CRP) (active disease >5 mg/L, in remission ≤5 mg/L)[31], platelets (active disease >400 $*10^9$/L, in remission ≤$400*10^9$/L) (Vumc a)[32] , leukocytes (active disease >$10*10^9$/L, in remission ≤$10*10^9$/L) (Vumc b)[33] and haemoglobin (active disease ≤10.5 g/dL, in remission >10.5 g/dL) (Vumc b)[33]. Physician's Global Assessment (PGA) (active or inactive) is an evaluation of the patient's wellbeing (clinical condition and symptoms) carried out by the treating physician.

STATISTICAL ANALYSIS

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 21.0. In performing our analysis, we adhered to the Consolidated Standards of Reporting Trial guidelines.[34]

With an effect size (ES) of 0.5 standard deviation, an alpha level of 0.05, and a power of 80%, at least 128 patients are required for the analysis and assuming an attrition rate of 10%, at least 142 patients need to be included. We based our sample size on RCTs among adult IBD-patients using the total-score of the IBDQ as the outcome variable.[11,12] In these studies Cohen's d (ES) ranged from d=0 to d=0.41. Because CBT is considered a more powerful intervention than those used in previous studies, we assumed an ES of 0.5 (moderate)[35], which amounts to a clinically relevant effect.[36,37] A 0.5 standard deviation corresponds to approximately 30 points on a scale ranging from 32 to 224.[38]

The primary analysis was the comparison of the mean IBDQ total-score at the 3.5-month follow-up between the randomised groups using an intention-to-treat (ITT) approach.[34] We refrained from the analysis of the pooled data of the experimental group and the data from the waiting-list control group while on CBT. This protocol deviation was decided upon prior to the analyses and was based on the observation during the study that in the waiting list group in total 12 of 59 patients dropped out. We argued that as a result the waiting list group, at the end of follow-up, was unlikely to be comparable to or representative of the group that started with CBT at randomization. Thus, the groups were

anticipated to be too heterogeneous to pool reliably and we therefore limited our analyses to the more conservative approach of using the data obtained in the parallel groups only.

Analyses of covariance were used to assess differences between the groups in follow-up scores of all continuous outcomes while accounting for their baseline-values. The effect of CBT on PGA was analysed as a dichotomous ('active' versus 'inactive') dependent variable using logistic regression and the result was presented as an odds ratio (OR). Minimization [26] variables were included as covariates in all these analyses. In additional analyses, we included baseline-factors that were not balanced between the randomised groups as covariates. Each of the above analyses was carried out in the completers group defined as those patients with an outcome IBDQ total-score at follow-up, 49 and 47 in number, in the CBT and control group, respectively. In addition, to the primary ITT analyses, we performed per protocol (PP) analyses including those patients who attended at least 5 CBT sessions. As patients who comply with the CBT may systematically differ from those who do not, we compared the PP-sample with the ITT-sample, also for baseline-characteristics by randomised group, and overall. The PP-analysis was not conducted for the biological markers and PGA due to small sample size (N=61).

As a sensitivity analysis we performed multiple imputation by chained equations (MICE) to handle missing values and re-analysed the data combining the results from 10 imputed data sets into pooled estimates. [39]

Using logistic regression we studied the missing data pattern by predicting a missing value for the outcome variables from the variables in the imputation model, those that were either in the effectiveness analyses or likely predictors of 'missingness'.[39] These analyses showed explained variances (Nagelkerke R2) around 68% suggesting that the outcome variable was missing at random (MAR) at least to some extent and consequently that multiple imputation may have reduced bias. However, data being missing not at random can never be excluded. We refrained from multiple imputation of the markers of disease-activity due to a small number of patients with available data.

To compare the relative magnitude of the effects, mean scores on the continuous outcomes were standardized to Cohen's *d* using the pooled standard deviation of the baseline-scores, for both the completers group and the MICE group. Cohen's *d* were calculated, with 0.3, 0.5 and 0.8 indicating a small, moderate and large ES, respectively. Effect estimates were presented with a 95% confidence interval (CI). The level of significance (alpha) was set at 0.05, two-sided.

Role of the funding source

The sponsor of the study, the Maag Lever Darm Stichting (MLDS) had no role in the study- design, data-gathering, data-analysis, data-interpretation, or in writing the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between January 2009 and November 2011 we screened 744 patients. Of these, 118 patients were randomised and provided baseline-data (Figure 1). At follow-up 96 participants (81%) provided data for analysis for the IBDQ total-score (ITT-completers).

Participants who provided follow-up information on the primary outcome (n=93) did not substantially differ from those who did not (n=25), with respect to baseline-characteristics (data available on request). A mean of 6 sessions (SD=3.00) was completed, with 73.7% (n=87) of participants completing at least five CBT-sessions.

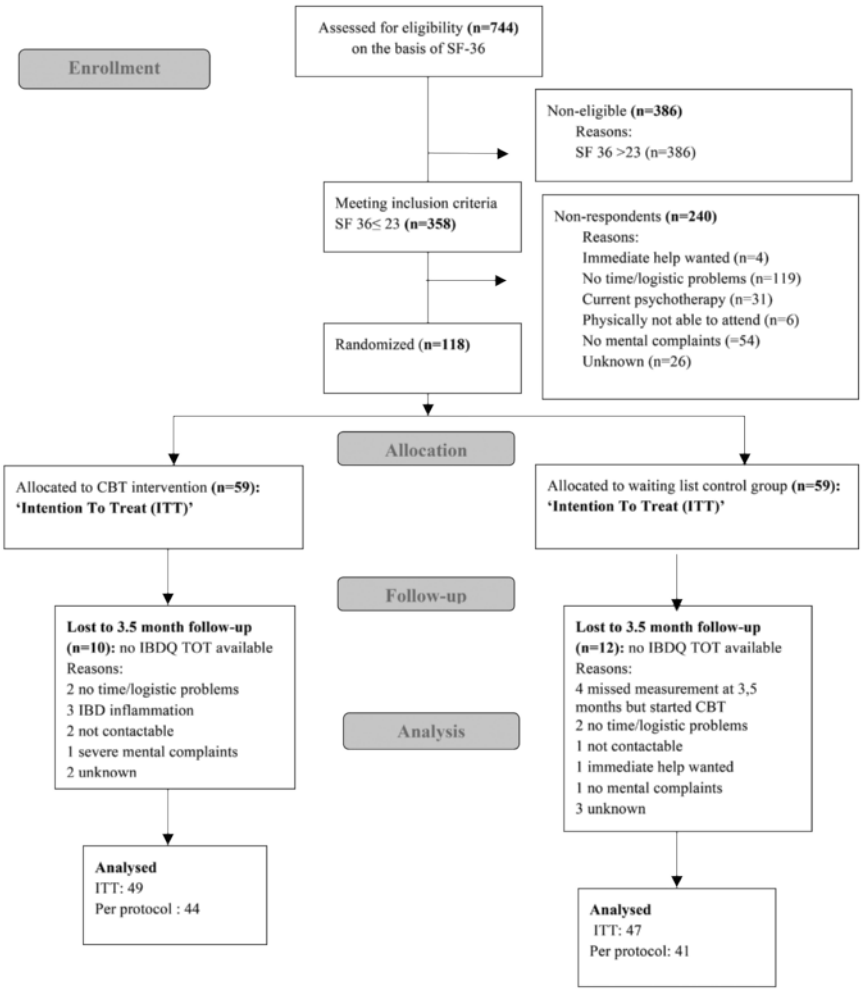

Figure 1. Flow diagram for IBD patients through the trial, including attrition

Table 1. Demographic and clinical baseline-characteristics of the ITT-group.

	Experimental Group (n=59)		Waitlist control Group (n=59)	
Characteristics	n (%)	M (range)	n (%)	M (range)
Gender				
Female	39 (66.1%)		36 (61.0%)	
Age in years (range)		39.4 (19.4-76.5)		38.7 (20.1-61.8)
Marital status				
In a relationship	30 (50.8%)		34 (57.6%)	
Level of education				
Low (Primary or Secondary)	33 (55.9%)		31 (52.5%)	
High (College or University)	26 (44.1%)		28 (47.5%)	
Employment				
Employed or studying	31 (52.5%)		41 (69.5%)	
Unemployed	28 (47.5%)		18 (30.5%)	
Sickleave	12 (20.3%)		12 (20.3%)	
Hospital type				
Academic	40 (67.8%)		39 (66.1%)	
Diagnosis				
Ulcerative colitis	24 (40.7%)		46 (44.1%)	
Crohn's disease	35 (59.3%)		33 (55.9%)	
Disease duration in years		11.9 (0.3-46.0)		10.4 (1.0-36.0)
Number of operations				
None	41 (69.5%)		32 (54.2%)	
≥1	18 (30.5%)		27 (45.8%)	
Stoma	3 (5.1%)		3 (5.1%)	
Medication				
Prednisone	14 (23.7%)		14 (23.7%)	
Antidepressants	4 (6.8%)		2 (3.4%)	
Family member(s) with IBD	14 (23.7%)		16 (27.1%)	
Current Axis 1 disorder	40 (67.8%)		43 (72.9%)	
Mood disorder	11 (18.6%)		13 (22.0%)	
Anxiety disorder	15 (25.4%)		22 (37.3%)	
Somatoform disorder	1 (1.7%)		0 (0.0%)	
Eating disorder	4 (6.8%)		2 (3.4%)	
Adjustment disorder	18 (30.5%)		18 (30.5%)	
Alcohol related disorder	1(1.7%)		1 (1.7%)	
Disorder related to substance abuse	0 (0.0%)		0(0.0%)	
Psychotic disorder	0 (0.0%)		0 (0.0%)	

ITT = intention to treat
Values are mean (SD) unless stated otherwise

The demographic- and clinical baseline-characteristics of the ITT-group (n=118) are summarized in Table 1. The percentage of unemployed or retired patients was higher in the experimental group (47.5%) than in the waitlist control group (30.5%). More participants of the waitlist control group (45.8%) had been operated on more than once due to IBD than in the experimental group (30.5%). All the other characteristics were similar in both groups. At baseline the mean outcome-scores did not differ between the two groups, with the exception of the IBDQ total-score which was slightly lower in the experimental group, however not significant (Table 2). No differences were observed between the randomised groups included in the PP-analysis (data not shown).

Table 2. Baseline outcome measures of the ITT-group.

	Experimental Group (n=59)	Waitlist control Group (n=59)
Mean IBDQ Total	144.70 (27.91)	152.21 (27.85)
Mean IBDQ Bowel	49.45 (10.11)	51.93 (10.30)
Mean IBDQ Systemic	18.02 (5.47)	19.66 (5.64)
Mean IBDQ Emotional	53.04 (11.80)	54.86 (11.32)
Mean IBDQ Social	24.20 (6.29)	25.77 (6.05)
Mean SF36 Physical	37.24 (7.04)	39.98 (9.39)
Mean SF36 Mental	36.27 (10.08)	36.70 (9.92)
Mean HADS anxiety	9.23 (4.25)	8.82 (3.72)
Mean HADS depression	7.46 (4.28)	7.45 (4.48)
Mean HADS total	16.70 (7.84)	16.27 (7.38)
Mean CES-D	22.23 (10.46)	20.23 (12.06)

ITT = Intention to treat
Values are mean (SD) unless stated otherwise

CBT exerted a statistically significant effect on the IBDQ total-score with a moderate ES (table 3). CBT had a significant effect on the IBDQ subscales Systemic and Emotional with a moderate and large ES respectively, while for subscales Bowel and Social, the effects were statistically insignificant.

CBT also significantly reduced the HADS total-score with a moderate ES and the anxiety and depression subscales with moderate ES. The percentage of the HADS total-scores ≥11 indicating a probable psychiatric disorder in the experimental group, decreased from 71.4% at baseline to 43.8% at follow-up. In the waitlist control group there was a decrease of 6.3%.

Table 3. ITT analyses completers* mean scores and differences between the experimental and waitlist control group at 3,5 month follow-up.

	Mean (SD)		Difference in means (95% CI), p-value			
			Completers estimate		MICE estimate	
Assessment	Experimental group (n=49)	Waitlist control group (n=47)	Difference (95% CI), p	ES (95% CI)	Difference (95% CI), p	ES (95% CI)
IBDQ total	168.12 (28.60)	152.98 (28.35)	18.16 (8.28 to 28.04), <**0.01**	0.64 (0.29 to 0.98)	15.80 (7.74 to 23.85) **<0.01**	0.55 (0.27 to 0.84)
IBDQ Bowel	53.63 (9.07)	51.45 (9.87)	3.16 (-0.46 to 6.77), 0.09	0.33 (-0.05 to 0.71)	2.61 (-0.3 to 5.52), 0.08	0.28 (-0.03 to 0.58)
IBDQ Systemic	22.20 (6.20)	19.89 (6.69)	3.17 (1.08 to 5.25), **<0.01**	0.49 (0.17 to 0.81)	2.88 (0.99 to 4.76), **<0.01**	0.45 (0.15 to 0.74)
IBDQ Emotional	64.80 (11.36)	55.13 (10.35)	10.00 (6.10 to 13.92), **<0.01**	0.92 (0.56 to 1.28)	8.48 (5.19 to 11.76), **<0.01**	0.78 (0.47 to 1.08)
IBDQ Social	27.49 (6.49)	26.51 (6.11)	1.68 (-0.47 to 3.83), 0.13	0.27 (-0.07 to 0.61)	1.52 (-0.29 to 3.32), 0.10	0.24 (-0.05 to 0.53)
SF36 Physical	40.92 (9.64)*	42.57 (10.51)	-0.39 (-3.52 to 2.74), 0.80	0.04 (-0.35 to 0.27)	-1.08 (-4.53 to 2.36), 0.53	-0.11 (-0.45 to 0.23)
SF36 Mental	47.68 (8.15)*	38.37 (9.26)	9.38 (6.09 to 12.67), **<0.01**	1.08 (0.70 to 1.45)	8.90 (5.68 to 12.12), **<0.01**	1.02 (0.65 to 1.39)
HADS Anxiety	6.06 (4.22)*	8.66 (3.75)	-2.33 (-3.71 to -0.95), **<0.01**	0.58 (-0.93 to -0.24)	-2.26 (-3.50 to -0.03), **<0.01**	0.57 (-0.88 to -0.01)
HADS Depression	4.33 (3.80)*	6.57 (4.02)	-1.89 (-3.18 to -0.59), **<0.01**	0.48 (-0.81 to 0.15)	-1.85 (-3.01 to -0.68), **<0.01**	0.47 (-0.77 to -0.17)
HADS Total	10.40 (7.32)*	15.23 (6.78)	-4.22 (-6.55 to -1.89), **<0.01**	0.60 (-0.93 to -0.27)	-4.11 (-6.08 to -2.14), **<0.01**	0.58 (-0.86 to 0.30)
CES-D	12.40 (8.95)*	18.91 (9.32)	-7.12 (-10.06 to -4.19), **<0.01**	0.78 (-1.10 to -0.46)	-5.81 (-8.58 to -3.04), **<0.01**	0.635 (-0.94 to -0.33)

Adjusted for baseline-value and stratification variables: gender, disease-type and academic vs peripheral
ITT completer is defined as having a follow-up score on the IBDQ TOT
*Based on n=48

The percentage of anxiety and depression HADS-scores ≥11 in the experimental group decreased from 35.7% and 25.0% at baseline to 10.4% and 4.2% respectively at follow-up. In the waitlist control group these figures were 2.3% and 3.4%, respectively.

Similarly, CBT significantly reduced CES-D scores with a large ES. It also had a significant effect on the MCS score of the SF-36 with a large ES, but not on its PCS. When we adjusted for unbalanced baseline-variables (employment and surgery) the results were similar. The MICE results for the above variables were essentially the same (Table 3). Where we restricted the analyses to patients who attended at least 5 CBT-sessions, the PP- sample, results were similar to those obtained in the ITT-group (table 4).

CBT also significantly reduced the HADS total-score and the anxiety and depression subscale-scores. The percentage of the HADS total-scores ≥11 indicating a probable psychiatric disorder in the experimental group, decreased from 69.8% at baseline to 45.5% at follow-up. In the waitlist control group there was a decrease of 10.3%. The percentage of anxiety and depression HADS-scores ≥11 in the experimental group decreased from 34.9% and 23.3% at baseline to 11.4% and 4.5%, respectively at follow-up. In the waitlist control group these figures were 1.7% and 1.9%, respectively.

Similarly, CBT significantly reduced CES-D scores. It also had a significant effect on the MCS score of the SF-36, but not on its PCS.

When we adjusted for unbalanced baseline-variables (employment and surgery) the results were similar. The MICE results for the above variables were essentially the same (table 4). The effect size differences between the PP-group and the ITT-group ranged from 0.02 to 0.04.

CBT did not reduce the level of IBD disease-activity biomarkers (mean adjusted difference as measured by CRP (-0.64; 95% CI -0.40 to 0.27; p=0.70), number of thrombocytes (-0.79; 95% CI -0.22 to 0.06; p=0.24), number of leukocytes (0.06 ;95% CI -0.11 to 0.23; p=0.46), haemoglobin level (5.81 ;95% CI -23.25 to 34.86; p=0.69) and active disease according to PGA (OR 0.64; p=0.57; 95% CI 0.13 to 3.04).

No adverse events related to the CBT were identified. In one case, action was taken as a result of the integrity checks by independent raters. The patient had a severe personality disorder and was referred to another therapist for long-term treatment two months after the final session and our post-assessment, thereby not affecting the results.

Table 4. *Per Protocol analyse completers* mean scores and differences between the experimental and waitlist control group at 3,5 month follow-up.*

	N		Mean (SD)		Difference in means (95% CI), p-value			
					ITT estimate		MICE estimate	
Assessment	Experi-mental Group	Waitlist control group	Experimental group	Waitlist control group	Difference (95% CI), p	ES (95% CI)	Difference (95% CI), p	ES (95% CI)
IBDQ Total	44	41	168.89 (28.56)	155.59 (26.81)	16.97(6.37 to 27.57), **<0.01**	0.61 (0.23 to 1.00)	16.15(6.17 to 26.14), **<0.01**	0.58 (0.22 to 0.94)
IBDQ Bowel	44	41	53.61 (9.13)	52.22 (9.87)	2.71(-1.09 to 6.51), 0.16	0.29 (-0.11 to 0.68)	2.39(-1.18 to 5.96), 0.19	0.25 (0.12 to 0.14)
IBDQ Systemic	44	41	22.64 (6.06)	20.34 (6.81)	3.11(0.85 to 5.36), **<0.01**	0.48 (0.13 to 0.83)	3.34(1.17 to 5.51), **<0.01**	0.52 (0.18 to 0.85)
IBDQ Emotional	44	41	64.82 (11.59)	56.22 (9.08)	9.42(5.21 to 13.62), **<0.01**	0.90 (0.50 to 1.31)	8.97(4.97 to 12.97), **<0.01**	0.86 (0.48 to 1.25)
IBDQ Social	44	41	27.82(6.41)	26.80 (5.79)	1.49(-0.83 to 3.81), 0.20	0.24 (-0.14 to 0.62)	1.29(-0.94 to 3.51), 0.26	0.21 (0.15 to 0.57)
SF36 Physical	44	41	41.39(42.17)	43.01 (10.40)	-0.45(-3.73 to 2.83), 0.79	-0.01 (-0.12 to 0.09)	-0.27(-3.48 to 2.94), 0.87	-0.01 (-0.11 to 0.10)
SF36 Mental	44	41	47.34(8.32)	38.80 (9.37)	9.40(5.86 to 12.94), **<0.01**	1.06 (0.66 to 1.46)	9.24(5.82 to 12.67), **<0.01**	1.04 (0.66 to 1.43)
HADS Anxiety	44	41	6.36(4.26)	8.49 (3.72)	-2.15(-3.65 to -0.66), **<0.01**	-0.54 (-0.91 to -0.17)	-2.23(-3.69 to -0.77), **<0.01**	-0.56 (-0.92 to -0.19)
HADS depression	44	41	4.41(3.88)	6.24 (4.05)	-1.66(-3.07 to -0.26), **0.02**	-0.42 (-0.77 to -0.07)	-1.75(-3.09 to -0.40), **0.01**	-0.44 (-0.78 to -0.10)
HADS Total	44	41	10.77(7.44)	14.73 (6.70)	-3.82(-6.37 to -1.27), **<0.01**	-0.54 (-0.90 to -0.18)	-3.97(-6.40 to -1.54), **<0.01**	-0.56 (-0.90 to -0.22)
CES-D	44	41	12.84(9.06)	18.49 (8.90)	-6.98(-10.16 to -3.79), **<0.01**	-0.78 (-1.13 to -0.42)	-6.99(-10.07 to -3.90), **<0.01**	-0.78 (-1.12 to -0.43)

* 'Per protocol analyse completers' is defined as completed equal or more than 5 sessions CBT
and having a follow up score on the IBDQ TOT **Adjusted for surgery and unemployment, respectively

DISCUSSION

CBT was effective in improving the specific IBD-related-QoL (primary outcome) and the mental aspects of generic QoL, anxiety and depressive symptoms (secondary outcomes) compared to the waitlist control group. Our findings contrast the reported mixed effects in aforementioned systematic reviews on the effect of psychotherapy for IBD-patients [11,12,13]

CBT had no effect on the disease-activity of either CD or UC or on physical components of QoL. Previous studies found that patients with depressive and anxiety symptoms run a greater risk of relapse of disease-activity .[5,40] Also, depression and anxiety have been found to influence the gastrointestinal inflammatory responses. [41] Therefore, we assumed that reducing depression and anxiety through CBT would diminish disease-activity. It should be noted that this study was not designed and powered to detect differences in disease activity. For this purpose larger cohorts and better biomarkers and/or endoscopic investigations are needed.

Overall, research has reported mixed effects of psychological interventions on disease-activity in other somatic illnesses. [42,43] A reason could be because these interventions do not incorporate directive stress-reducing interventions, such as relaxation techniques or hypnotherapy .[44] However, studies combining CBT with these techniques showed mixed results on physical outcomes in IBD-patients.[12] Therefore, more research is needed to investigate the effectiveness of relaxation techniques complementary to CBT.

Depression with a co-morbid chronic somatic illness increases the likelihood of poorer outcomes and (psychological) treatment response .[45,46] Less is known about the impact of anxiety on treatment outcomes in chronic medical illness. In this study 70.3% of the patients had an current Axis-1 disorder. We mainly found patients with depressive disorders (20.3%), anxiety (31.4%) and adjustment disorders (30.5%).

Our study has several strengths. The results covered a wide spectrum of IBD-patients since enrollment took place in academic and peripheral medical centres. Patients were screened according to the SCID-I at baseline, to assess not only depressive and anxiety complaints but also mental health disorders. Our study focused on IBD patients with poor mental QoL who were expected to have a high-risk prevalence of psychiatric disorders and to be in need of mental care. Furthermore, all therapists administering the standardized CBT followed an IBD-training-program and regularly received supervision from the researcher. The treatment they administered was also recorded and checked against the Check Treatment Manual.

Some limitations of this study merit attention. Blinding was not possible for our primary and secondary outcomes as these were assessed using self-report questionnaires by patients (except for biological assessments). Also, our study was somewhat underpowered for the primary outcome (n=96 for the complete case analysis rather than the planned n=128). Nevertheless, we observed statistically significant results for most outcomes and our sensitivity analysis using multiple imputation showed similar effect sizes to the

complete case analysis indicating little or no bias due to attrition. Finally, a wait-list is not the optimal control condition.[47] Therefore, future studies should compare the current CBT for IBD with a treatment as usual group or an active control group, such as CBT that has not been adapted to specifically for IBD patients.

Conclusions: CBT was effective in improving the specific IBD-related QoL and in decreasing anxiety and depression. IBD-patients require integrated medical- and psychological treatment.[48] Clinicians should incorporate screening on poor mental QoL [21] and refer IBD patients to a psychologist offering CBT.

RESEARCH IN CONTEXT

Systematic review

The search for this study was carried out from January 2010 till January 2016. We used the same search strategy as in the Cochrane review conducted by Timmer et. al.[11] in April 2011 but excluding the search term 'study design' in order to minimize information bias. Full details of the research are available by request from the first author. This led to 737 articles. We finally identified two reviews [12,13] and three RCTs [21,49,50] (one of them is still recruiting [49]). We only included reviews incorporating CBT and adults. We excluded articles based on children and adolescents, supportive therapy and e-health.

Interpretation

This is the first study that examines the effect of CBT on four highly relevant outcomes in a large group of patients with IBD: QoL, depression, anxiety and disease-activity. We found that CBT improves well-being and reduces anxiety and depression in adult IBD-patients with poor mental quality of life. Therefore, we suggest that clinicians should consider incorporating screening for poor mental QoL [21] and refer IBD-patients to psychologists offering CBT.

CONTRIBUTORS

FBE was the chief investigator grant holder of the trial. She drafted the final manuscript (which was added and modified by all other authors), wrote the treatment manual for the used CBT-intervention (which was added and modified by CLHB) and was responsible for the training and supervision of the psychotherapists. MAGS is the study's principal investigator. The statistical analysis plan was set up by FBE, CLHB and HB was responsible for statistical analysis and reporting (adviser statistical analyses). MAG, PS, RS, and CLHB supervised the study and contributed to the design of the study and the analytic strategy. MAG, PS, RS, FBE and CLHB were responsible for the funding. KS supported in literature searches, reference preparation and reviewed earlier drafts of the article. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests. FBE received an unrestricted research grant from Scheringh and Plough of 20.000 euros to study psychological factors in IBD.

ACKNOWLEDGMENTS

First, we would like to thank all participating patients with IBD who took part in this study. The research is externally funded by a Grant Application of the noncommercial Stomach Liver Bowel Foundation (Maag Lever Darm Stichting (MLDS)) from the Netherlands, that carried out the peer review of the proposal (registration number: WO 07-45). We thank all medical specialists (gastro enterologists), support staff, and management of the Academic Medical Centre Amsterdam (AMC), Flevo Hospital, Slotervaart Hospital and VU University Medical Centre Amsterdam (VUmc) for enabling the RCT. We would also like to thank the medical centres Leiden University Medical Centre (LUMC) and The Radboud university medical centre for initially participating in this study. Additionaly, we thank all cognitive behavioural clinical psychologists Truus Wilterdink, Ineke Lauwen, Eva Zuijderland, Annemieke Osendarp, Yvonne Kieviet, Anne Winters, Iris Panders, Katelijne Cornelisse, Dorine van der Schaar, Annemieke Ritzen, Debbie Been, Eric Aalsma, Walter de Vries, Heleen Grandia, Ralph Tinnemans, Aart Beekman, Marjolein Hanson, and Maria Goog who administered the CBT-intervention.

REFERENCES

1. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, Benchimol EI, Panaccione R, Ghosh S, Barkema HW, Kaplan GG. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterol 2012; 142(1): 46-54.
2. Kilcoyne Aoife, Kaplan Jess L, Gee Michael S. Inflammatory bowel disease imaging: Current practice and future directions. World J Gastroenterol. Jan 21, 2016; 22(3): 917-932
3. Zhang YZ, Li YY., 2014. Inflammatory bowel disease: Pathogenesis. World J Gastroenterol , 20(1): 91-99.
4. Bennebroek Evertsz' F, Thijssens NA, Stokkers PC, Grootenhuis MA, Bockting CLH, Nieuwkerk PT, Sprangers MAG. Do inflammatory Bowel Disease patients with anxiety and depressive symptoms receive the care they need? J Crohn's Colitis 2012; 6(1): 68-76.
5. Mittermaier C, Dejaco C, Waldhoer T, Oefferlbauer-Ernst A, Miehsler, W. Impact of depressive mood on relapse inpatients with inflammatory bowel disease: A prospective 18- month follow-up study. Psychosom Med 2004; 66: 79-84
6. Walker JR, Ediger JP, Graff LA, Greenfeld JM, Clara I, Lix L, Rawsthorne P, Miller N, Rogala L, McPhail CM, Bernstein CN. The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. Am J Gastroenterol 2008; 103: 1989–97.
7. Katon W, Lin EHB, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry 2007; 29(2): 147-55.
8. Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Andrews JM and Holtmann GJ. Controversies Surrounding the Comorbidity of Depression and Anxiety in Inflammatory Bowel Disease Patients: A Literature Review. Inflamm Bowel Dis 2007; 13(2): 225-34.
9. Van Straten A, Geraedts A, Verdonck-de Leeuw I, Andersson G and Cuijpers P. Psychological treatment of depressive symptoms in patients with medical disorders: a meta- analysis. J Psychosom Res 2010; 69(1): 23-32.
10. Osborn RL, Demoncada AC, Feuerstein M. Psychological interventions for depression, anxiety and quality of life in cancer survivors: meta-analyses. Int J Psychiatry in Med 2006; 36 (1): 13-34.
11. Timmer A, Preiss JC, Motschall E, Rücker G, Jantschek G, Moser, G. Psychological interventions for treatment of inflammatory bowel disease (Review). Cochrane Database Syst Rev 2011; 5: 1-132.
12. McCombie AM, Mulder, RT, Gearry RB (2013). Psychotherapy for Inflammatory Bowel Disease: A review and update. J Crohn's Colitis 2013; 7(12): 935-49.
13. Knowles SR, Monshat K, Castle DJ. The efficacy and methodological challenges of psychotherapy for adults with inflammatory bowel disease: a review. Inflamm Bowel Dis 2013; 19: 2704-2715.
14. Wahed M, Corser M, Goodhand JR, Rampton DS. Does psychological counselling alter the natural history of inflammatory bowel disease? Inflamm Bowel Dis 2010; 16: 664-9.
15. Keefer L, Kiebles JL, Martinovich Z, Cohen E, Van Den Burg A, Barrett TA. Behavioral interventions may prolong remission in patients with inflammatory bowel disease. Beh Res Ther 2011; 49(3): 145-50.

16. Keefer L, Doerfler B, Artz C. Optimizing management of Crohn's disease within a project management framework: results of a pilot study. Inflamm Bowel Dis 2012; 18(2): 254-60.
17. Schwarz SP, Blanchard EB. Evaluation of a psychological treatment for inflammatory bowel disease. Behav Res Ther 1991; 29: 167-177.
18. Mussell M, Bocker U, Nagel N, Olbrich R, Singer MV. Reducing psychological distress in patients with inflammatory bowel disease by cognitive-behavioural treatment; exploratory study of effectiveness. Scand J Gastroenterol 2003; 38: 755-762.
19. Langhorst J, Mueller T, Luedtke R, Franken U, Paul A, Michalsen A, Schedlowski M, Dobos GJ, Elsenbruch S. Effects of a comprehensive life-style modification program on quality-of-life in patients with ulcerative colitis; a twelve-month follow-up. Scand J Gastroenterol 2007; 42: 734-745.
20. Diaz SibajaMA, Comeche Moreno MIMas Hesse B. Protocolized cognitive-behavioural group therapy for inflammatory bowel disease. Rev Esp Enferm Dig 2007; 99: 593-598.
21. Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-behavioural therapy has no effect on disease activity but improves quality of life in subgroups of patients with inflammatory bowel disease: a pilot randomised controlled trial. BMC Gastroenterol 2015;15:54.
22. Bennebroek Evertsz' F, Bockting CL, Stokkers PC, Hinnen C, Sanderman R, Sprangers MAG. The effectiveness of cognitive behavioral therapy on the quality of life of patients with inflammatory bowel disease: multi-center design and study protocol (QL!C- study). BMC Psychiatry 2012 Dec 14; 12: 227.
23. Ware JE . The MOS 36-item Short-Form health survey. Boston: Health Institute, 1992.
24. First MB, Spitzer, RL, Gibbon, M, Williams JBW. Gestructureerd klinisch interview voor de vaststelling van DSM-IV As I Stoornissen. Lisse: Swets & Zeitlinger B.V, 1999.
25. NTR (TC=1869) Nederlands Trial Register. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1869
26. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975; 31(1): 103-15.
27. Beck AT. The Current State of Cognitive Therapy A 40-Year Retrospective. Arch Gen Psychiatry 2005; 62: 953-59
28. Russel MGVM, Pastoor CJ, Brandon S, Rijken J, Engels LGJB, Van der Heijde DMFM, Stockbrügger RW. Validation of the Dutch translation of the inflammatory bowel disease questionnaire (IBDQ): a health-related quality of life questionnaire in inflammatory bowel disease. Dig 1997; 58(3): 282 - 88.
29. Zigmond AS, Snaith RP (1983). The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica 67, 361-70.
30. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement 1977; 3: 385-401.
31. Ousallah A, Laurent V, Bruot O, Guéant JL, Regent D, Bigard MA, Peyrin-Biroulet L. Additional benefit of procalcitonin to C-reactive protein to assess disease activity and severity in Crohn's disease. Aliment Pharmacol Ther 2010; 32: 1135–44.

32. Vumc a: Laboratoriumwaarden en referentiebepalingen (http://internet-extra.vumc.nl/referentiewaarden/BepalingDetail.asp?BepalingId=471http://labboekje/index.cfm?fuseaction=Labviewer.showbepaling&bid=862). Accessed 23 Januari 2014.
33. Vumc b: Laboratoriumwaarden en referentiebepalingen (http://internet-extra.vumc.nl/referentiewaarden/BepalingDetail.asp?BepalingId=472http://labboekje/index.cfm?fuseaction=Labviewer.showbepaling&bid=559) Accessed 23 January 2014.
34. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Deveraux PJ, Elbourne D, Egger M, Altman DG. CONSORT explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 23: 340.
35. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Mahwah, NJ: Lawrence Erlbaum Associates,1988.
36. Norman, GR, Sloan JA, Wyrwich KW. Interpretation of Changes in Health-related Quality of Life: The Remarkable Universality of Half a Standard Deviation. Med Care 2003; 41(5): 582-92.
37. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008; 61: 102-9.
38. McColl E, Han SW, Barton JR, Welfare MR. A comparison of the discriminatory power of the Inflammatory Bowel Disease Questionnaire and the SF-36 in people with ulcerative colitis. Qual Life Res 2004; 13: 805-11.
39. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011; 30(4): 377-99.
40. Mardini HE, Kip KE, Wilson JW. Crohn's disease: a two-year prospective study of the association between psychological distress and disease activity. Dig Dis Sciences 2004; 49: 492–7.
41. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. Gut 2005; 54(10): 1481-91.
42. Whalley B, Rees K, Davies P, Bennett P, Ebrahim S, Liu Z, West R, Moxham T, Thompson DR, Taylor RS. Psychological interventions for coronary heart disease. Cochrane Database Syst Rev 2011; 10(8).
43. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet 2004; 363: 1589-97.
44. Keefer L, Taft TH, Kiebles JL, Martinovich Z, Barrett TA, Palsson OS. Gut-directed hypnotherapy significantly augments clinical remission in quiescent ulcerative colitis. Aliment Pharmacol Ther 2013; 38(7): 761-71.
45. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, third edition. October 2010; 152: 1170.
46. National Collaborating Centre for Mental Health. Depression in adults with a chronic physical health problem. Treatment and management. NICE clinical guideline 91 ed. London: The National Collaborating Centre for Mental Health, 2009.
47. Handley MA, Schillinger D, Shiboski S. Quasi-Experimental Designs in Practice-based Research Settings: Design and Implementation Considerations. JABFM Sep–Oct 2011; 24(5): 589-96

48. Fava GA, Ruini C, Tomba E, Wise TN. The biopsychosocial factor. Psychother Psychosom 2012; 81: 1- 4.

49. Mikocka-Walus AA, Turnbull D, Holtmann G, Andrews JM. An integrated model of care for inflammatory bowel disease sufferers in Australia: Development and the effects of its implementation. Inflamm Bowel Dis 2012; 18: 1573-1581.

50. Mizrahi MC, Reicher-Atir R, Levy S, Haramati S, Wengrower D, Israeli E, Goldin E. Effects of guided imagery with relaxation training on anxiety and quality of life among patients with inflammatory bowel disease. Psychol Health 2012; 27 (12): 1463-1479.