

The Cost-effectiveness of Psychotherapy and Paroxetine for Severe Irritable Bowel Syndrome

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Background & Aims: Psychotherapy and antidepressants are effective in patients with severe irritable bowel syndrome (IBS), but the cost-effectiveness of either treatment in routine practice has not been established. **Methods:** Patients with severe IBS were randomly allocated to receive 8 sessions of individual psychotherapy, 20 mg daily of the specific serotonin reuptake inhibitor (SSRI) antidepressant, paroxetine, or routine care by a gastroenterologist and general practitioner. Primary outcome measures of abdominal pain, health-related quality of life, and health care costs were determined after 3 months of treatment and 1 year later. **Results:** A total of 257 subjects (81% response rate) from 7 hospitals were recruited; 59 of 85 patients (69%) randomized to psychotherapy and 43 of 86 (50%) of the paroxetine group completed the full course of treatment. Both psychotherapy and paroxetine were superior to treatment as usual in improving the physical aspects of health-related quality of life (SF-36 physical component score improvement, 5.2 [SEM, 1.26], 5.8 [SEM, 1.0], and -0.3 [SEM, 1.17]; $P < 0.001$), but there was no difference in the psychological component. During the follow-up year, psychotherapy but not paroxetine was associated with a significant reduction in health care costs compared with treatment as usual (psychotherapy, \$976 [SD, \$984]; paroxetine, \$1252 [SD, \$1616]; and treatment as usual, \$1663 [SD, \$3177]). **Conclusions:** For patients with severe IBS, both psychotherapy and paroxetine improve health-related quality of life at no additional cost.

Irritable bowel syndrome (IBS) is the major cause of referrals to gastroenterology clinics in the western world¹ at an estimated cost of \$8 billion per year in the United States.² Severe IBS leads to a 3-fold increase in work absenteeism and doctor visits and to severely impaired health-related quality of life.^{3,4} Current pharmacologic therapies directed at the gut are disappointing in this group.^{5,6} The prevalence of anxiety and depressive disorders is high in patients with severe IBS, and both

psychotherapy and tricyclic antidepressant drugs have been shown to be more effective than placebo.⁷⁻⁹ However, the role of these treatments in everyday practice has not been defined.¹⁰ To do so requires a study of cost-effectiveness, which, unlike a short-term efficacy trial, assesses how many patients will comply with treatment in the usual clinical setting together with measures of costs and outcome.¹¹ A study of cost-effectiveness therefore uses a comparison group receiving conventional treatment to determine the usual costs and outcome associated with the condition.¹¹ A cost-effectiveness study for IBS is relevant for health care planning because of the large numbers of patients involved, the prolonged period of taking medication, and the markedly impaired health-related quality of life (including time off work).

Tricyclic antidepressants have been used for IBS in previously reported studies,⁹ but all efficacy studies have been short-term (up to 3 months) and severe IBS is a chronic disorder.⁴ Tricyclic antidepressants are now being replaced in clinical practice by the newer specific serotonin reuptake inhibitor (SSRI) class of antidepressants because SSRIs are as effective, safer, and better tolerated with fewer unwanted side effects.^{12,13} We therefore chose to use SSRI therapy in this study because we believed the results would be more relevant to current therapeutic practice, although data clearly establishing the efficacy of SSRI antidepressants in patients with IBS had not been established when this study commenced.⁹

Based on our previous study that showed psychodynamic interpersonal therapy to be effective in a selected group of patients with IBS,⁷ we were interested in the benefit of this psychological treatment in a more repre-

Abbreviations used in this paper: IBS, irritable bowel syndrome; SSRI, selective serotonin reuptake inhibitor.

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sentative sample of patients with severe IBS. We also wished to compare the cost-effectiveness of psychotherapy and paroxetine (an SSRI antidepressant) in patients with severe IBS. The trial was restricted to patients with severe IBS who had not responded to usual pharmacologic treatments, because these are the patients for whom psychological treatments are believed to be most appropriate.^{7,14} We sought to test whether, compared with usual treatment, psychotherapy or paroxetine would not only provide effective pain relief but also reduce health and nonhealth costs. We measured effectiveness in terms of abdominal pain as well as physical and psychological components of health-related quality of life,^{15–17} and we included health care and other costs, including time lost from work. We examined whether improved functioning (health-related quality of life) could be explained in terms of reduced psychological distress.

The trial aimed to test the following hypotheses in a representative sample of patients with severe IBS: (1) that psychotherapy and paroxetine would be superior to treatment as usual in reducing abdominal pain and improving health-related quality of life, (2) that the improvements following psychotherapy and paroxetine would be achieved without additional costs (i.e., that the additional costs of these treatments would be offset by reduced health care costs during the year after treatment had ended), and (3) that improvement would be least in patients with a reported history of sexual abuse or who showed no improvement in psychiatric symptoms during the trial.

Materials and Methods

Participants

Patients were recruited from 3 secondary-level and 4 tertiary-level gastroenterology clinics around Manchester and Sheffield in England. All potentially eligible patients identified from clinic records were interviewed by a research psychiatrist. Those who fulfilled the following entry criteria were invited to participate in the trial: (1) Rome I criteria for IBS satisfied¹⁸; (2) duration of symptoms >6 months; (3) failure to respond to “usual” medical treatment, including antispasmodics and laxatives or antidiarrheal medication administered for a minimum of 3 months; (4) severe abdominal pain, defined as >59 on a visual analogue scale⁴; (5) no contraindication to either psychotherapy or paroxetine; (6) ability to complete the study questionnaires; and (7) aged 18–65 years. “Severe” IBS refers to patients who fulfill criteria 2–4.

Ethics committee approval was obtained from each relevant health authority. After full explanation, all patients gave their written consent to participate.

Interventions

The psychotherapy was psychodynamic interpersonal therapy similar to that described in our previous trial.^{7,19} Patients received one long (approximately 2 hours) and 7 shorter (45 minutes) individual sessions over 3 months. They were encouraged to discuss their symptoms in depth; emotional factors were explored, and links between symptoms and emotional factors were identified. Three therapists (2 at Manchester and one at Sheffield) were trained by a member of the study team (E.G.) using a manual and a videotaped training package; continued conformity by the therapist to the model was ensured by weekly supervision with E.G.

The SSRI treatment comprised paroxetine 20 mg orally each day for 3 months, prescribed and monitored either by the patient’s gastroenterologist or general practitioner.

For treatment as usual, patients continued to be seen either by their gastroenterologist and/or general practitioner, using whatever management was deemed appropriate throughout the 15 months of the study.

After 3 months of treatment, all patients receiving psychotherapy or paroxetine returned to their general practitioner, who decided what further management was required over the next year.

Outcomes

Patients were assessed at trial entry, at the end of the 3-month treatment period, and 1 year after the end of treatment by researchers who were blinded to treatment group.

At trial entry, demographic data and detailed symptomatic and treatment histories were obtained. Current psychiatric disorder was assessed using Schedules for Clinical Assessment in Neuropsychiatry interview.²⁰ This is a standardized, objective interview for which the psychiatrist is trained before administration. A reported history of sexual abuse was recorded using the Drossman questionnaire, which was administered by the research psychiatrist.²¹ In this report, sexual abuse is defined as patients reporting that they had been forced to have sex against their will either as a child or adult. Psychiatric disorder and a reported history of sexual abuse were used as predictor variables.

IBS symptoms were recorded using (1) a visual analogue scale of current severity of the abdominal pain,⁴ (2) a record of the number of days in the previous month with abdominal pain,⁴ and (3) overall change in symptoms according to 3 categories (improved, same, or worse). The first was taken as a primary outcome variable.

Health-related quality of life was measured by the patient completing the SF-36.²² This has been shown to correspond closely to a patient’s own rating of severity of IBS¹⁶ and is suitable for use in clinical trials.^{16,23} Data are provided as physical and mental component scores.²⁴ The mean score on each for the general population is 50, with a standard deviation of 10. A low physical component score indicates limitations of

work and other activities, severe pain, and poor general health. A low mental component score indicates psychological distress and social disability due to emotional problems and fatigue.²⁴ The SF-36 physical component score was used as a primary outcome measure as it is widely used and it would measure all aspects of health-related quality of life that might improve following psychological treatments.

Psychological distress was measured using the global severity index SCL-90²⁵ as a mediating variable.

Costs. Activity data were taken directly from the patient's hospital and primary care notes because all patients received professional health care solely from the U.K. National Health Service. Other costs were derived from the patient interview using the Client Service Receipt Inventory.²⁶ Unit costs were adjusted to 1997/1998 prices, and all costs incurred after 12 months were discounted at 6%. Conversion from pounds sterling to dollars was made at the rate operating at the time of the study (£1 = \$1.6).

Direct health care costs were derived by applying an appropriate unit cost (from the relevant local service providers or national data sources^{27,28}) to each recorded contact or episode of care. Hospital costs included inpatient days as well as outpatient, day-patient, and accident and emergency department attendances. Nonhospital costs included all primary care contacts (general practitioner surgery and home visits, practice nurse, and practice-based counselors), domiciliary care services (National Health Service and local authority) and day centers, and use of alternative therapies and prescribed medications. Direct health care costs were used as a primary outcome variable.

The additional treatment costs for psychotherapy were calculated using cost per minute of the therapist's time and supervision time, including on-costs and overhead costs. Costs for use of paroxetine were calculated from the number of prescriptions and the published U.K. price.²⁸

Direct non-health care costs were also measured. These included travel costs and additional patient expenditure as a result of the illness, nonprescription medication, and any additional expenditure relating to housework, child care, or personal care. Productivity costs were also measured by applying the patient's wage rate to the number of days lost either due to illness or clinic attendance. Patients on invalidity benefits were not included in this analysis, but the number of people receiving benefits at the beginning and end of the trial was recorded.

At the 3-month and 15-month interviews, the patients were asked a global question as to whether their IBS symptoms had improved, stayed the same, or worsened since the start of the trial.

Sample size. The estimated sample size for this trial was 85 in each group, based on the degree of improvement in a visual analogue scale of abdominal pain found in our previous study of psychotherapy.⁷

Randomization

After baseline assessment, patients were stratified by hospital and by pain severity (using the visual analogue scale) into "severe" (>59 to <89) or "very severe" pain (≥ 89)⁴ to ensure that no group included an excess of patients with very severe pain. Randomization was then performed in blocks of 12 subjects using randomization lists supplied by the trial statistician (B.T.) drawn from a computer-generated series of random numbers. The randomization list was maintained by the study administrator.

Allocation concealment. Allocation was disclosed to the recruiting clinician only after baseline assessments were completed and consent was obtained.

Implementation. The randomization lists were provided by the trial statistician (B.T.) before recruitment commenced. When patients had been assessed and accepted into the trial, they were then allocated to a treatment group by the trial administrator using the next slot on the appropriate randomization list.

Blinding (masking). Treatment allocation and compliance were not revealed to the researchers conducting the baseline and follow-up assessments until after the study was completed and all data had been entered into the database and verified. Clinicians involved in delivery of treatments worked independently of those involved in collection of follow-up data; hence, data were collected from all patients at all times wherever possible, regardless of whether the patients received the full course of treatment.

Statistical Methods

Baseline variables were compared using the χ^2 test, Kruskal-Wallis test, or one-way analysis of variance as appropriate. For the primary and secondary outcome measures, the effect of the 2 main centers (Manchester and Sheffield) was tested using a generalized linear model with repeated measures, with centers as random between subject effects, treatments as fixed between subject effects, time as a repeated measure, and all interactions. Because there was no significant center by treatment interaction for any variable, the data from the 2 centers have been combined.

Primary analyses. An intention-to-treat analysis was used to compare the outcome data for the 3 groups using all available data. Analysis of covariance was used in the comparisons of follow-up assessments to adjust for any baseline differences. When the difference between the 3 groups was significant at the 5% level, post-hoc Bonferroni adjusted pairwise comparisons were made. The cost data are presented as mean weekly costs to adjust for slight differences in the length of time between baseline and the 1-year follow-up interview. Due to the highly skewed nature of cost distributions, bootstrap methods were used to compare treatment groups with respect to costs.²⁹ These results are presented as 95% bias-corrected confidence intervals for the difference in mean costs of the intervention group and the treatment-as-usual group, having

Table 1. Comparison Between the 3 Treatment Groups at Baseline

Categorical variables	Psychotherapy (n = 85)		Paroxetine (n = 86)		Treatment as usual (n = 86)		Comparison $\chi^2/df/P$
	No.	%	No	%	No	%	
Center							
Manchester	46	54	46	54	47	55	0.02/2/0.99
Sheffield	39	46	40	46	39	45	
White ethnicity	82	97	86	100	85	99	3.6/2/0.17
Male/Sex	17	20	16	19	19	22	0.3/2/0.85
Marital status							
Single	21	25	17	20	12	14	
Married/cohabiting	52	61	54	63	63	73	4.3/4/0.36
Separated/divorced/widowed	12	14	15	17	11	13	
Education of 12 years or more	46	54	47	55	47	55	0.01/2/1.0
Unemployed due to poor health	29	34	20	23	21	24	3.1/2/0.22
Psychiatric disorder (confirmed by SCAN)	41	48	40	47	40	47	0.1/2/0.97
Rome diagnosis							
Other (general)	36	42	45	52	43	50	
Diarrhea predominant	27	32	21	24	26	30	2.6/4/0.63
Constipation predominant	22	26	20	23	17	20	
Severe sexual abuse	11	13	12	14	8	9	1.0/2/0.62

SCAN, Schedules for Clinical Assessment in Neuropsychiatry.

adjusted for any differences before baseline. One thousand replications were used in each analysis. Further analyses were performed using the missing data software package Solas,³⁰ whereby missing values for follow-up assessments were imputed based on the correlations that exist between baseline and follow-up assessments.

Ancillary analyses. In addition to the intention-to-treat analysis, a per protocol analysis was performed including only fully compliant patients ("protocol completers") who attended all 8 sessions of psychotherapy or completed 12 weeks of treatment with paroxetine. Bonferroni adjustments were also made to account for multiple outcome measures.

To assess whether improvement in the physical component of health-related quality of life could be explained in terms of reduced psychological distress, an analysis of covariance was performed. The change in SF-36 physical component score

between baseline and 1 year follow-up was compared for the psychotherapy, paroxetine, and usual treatment groups with age, sex, baseline physical component score, and change in SCL-90 global index score as covariates.

To identify the variables that predicted improvement in health-related quality of life in the psychotherapy and paroxetine groups, each of the variables shown in Tables 1–3 was analyzed in relation to the change score of the SF-36 physical component score. All of the variables, which were associated at $P < 0.2$, were entered into a multiple regression analysis with change in SF-36 physical component score from baseline to 15 months follow-up as the dependent (outcome) variable.

All analyses were performed using Statistics Package for the Social Sciences for Windows 98, version 9, except bootstrapping analysis (which used STATA) and analyses with missing values imputed (which used Solas).

Table 2. Comparison Between the 3 Treatment Groups at Baseline

Scored, non-normal variables	Psychotherapy (n = 85)		Paroxetine (n = 86)		Treatment as usual (n = 86)		Kruskal-Wallis <i>P</i>
	Median	IQR	Median	IQR	Median	IQR	
Days with restricted activity in the past year	90	14–211	60	6–225	131	27–365	0.16
No. of visits to the doctor in the past 6 months	6	3–9	5	3–9	6	3–10	0.51
Years of bowel problems	8	4–13	8	5–17	8	3–18	0.68
No. of days with pain in the past 30 days	30	22–30	30	15–30	30	15–30	0.053

IQR, interquartile range.

Table 3. Comparison Between the 3 Treatment Groups at Baseline

Normally distributed variables	Psychotherapy (n = 85)		Paroxetine (n = 86)		Treatment as usual (n = 86)		ANOVA P
	Mean	SEM	Mean	SEM	Mean	SEM	
Age (yr)	39.9	1.36	39.4	1.15	40.6	1.33	0.80
Visual analogue scale for abdominal pain	67.8	1.81	67.59	1.62	66.65	1.73	0.88
SF-36 physical component score	38.2	1.04	36.7	1.24	38.3	1.24	0.55
SF-36 mental component score	39.9	1.46	41.0	1.36	40.6	1.42	0.87
SCL-90 global severity index	0.90	0.070	0.96	0.073	0.83	0.064	0.39

Results

Recruitment

Recruitment of patients took place from October 1994 to October 1997, with the final follow-up assessment completed in February 1999.

Baseline Data

A total of 257 of 317 eligible patients (81%) were recruited. There were no differences in demographic and diagnostic variables between those patients who agreed and those who declined to enter the trial. Details of the treatment groups on entry to the trial are shown in Tables 1–3. Twenty-nine percent had diarrhea-predominant IBS, 23% had constipation-predominant IBS, and 48% had general IBS. During the 3 months before trial entry, 92.6% were using antispasmodic medications, 26% were using antidiarrheal medications, and 38% were taking one or more additional analgesics. A total of 60% were taking laxatives, and 16% were taking motility stimulants; 29% had used alternative therapies previously. Forty-seven percent of the sample had a definite psychiatric diagnosis (principally anxiety or depressive disorders). Thirty-one (12%) reported a history of sexual abuse.

Participant Flow

Of the 85 patients (69%) randomized to psychotherapy, 59 completed all 8 sessions, and 43 of the 86 patients (50%) randomized to paroxetine completed the 12-week course (χ^2 , 5.91; *df*, 1; *P* = 0.013) (Figure 1). In the antidepressant group, 14 patients did not take the medication; they had agreed to enter the trial but refused to take the medication once it was prescribed by the general practitioner or gastroenterologist. A further 29 subjects discontinued antidepressants because of side ef-

fects (most commonly sedation, light-headedness, sexual or sleep problems, nausea, and diarrhea); 20 discontinued them during the first 6 weeks of treatment, and a further 9 did so between 6 and 12 weeks of the treatment period. Twelve people randomized to psychotherapy did not commence psychotherapy, and 14 patients dropped out of therapy without explanation. There were no significant differences in baseline measures between patients who completed their course of treatment and those who did not in either of the 2 treatment groups.

At 1-year follow-up, pain and SF-36 scores were recorded for 90% and 75% of patients, respectively; there were no significant differences in baseline scores between patients who completed and did not complete these follow-up questionnaires in any of the 3 treatment groups. Direct health care costs were recorded for 97% of patients.

Outcomes and Estimation

IBS pain. After 3 months, all 3 groups recorded a reduction in severity of abdominal pain and number of days of pain (Table 4 and Figure 2). The between-group differences were not significant for pain severity, but the paroxetine group showed a significantly greater reduction in days with pain than the treatment-as-usual group (Table 4). At 1-year follow-up, both the severity and frequency of abdominal pain had improved from baseline for all 3 groups, but there were no significant differences between groups (Table 4).

Health-related quality of life. *Physical component.* After 3 months, both the psychotherapy and paroxetine groups showed a small improvement in the physical component score compared with usual treatment. At 1-year follow-up, both intervention groups showed a

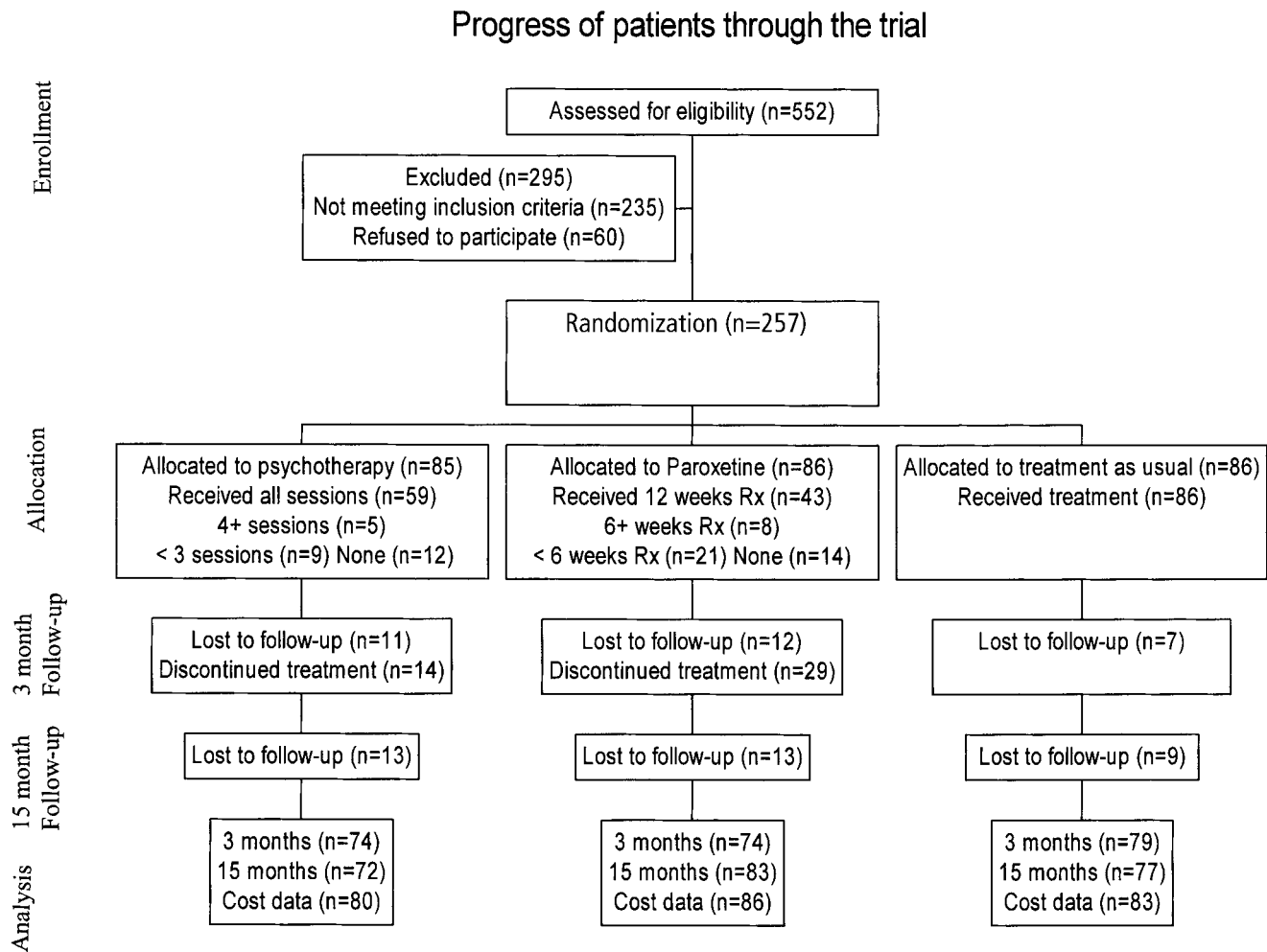


Figure 1. CONSORT statement showing progress of patients through the trial.

significant improvement over usual treatment ($P < 0.001$) (Table 4).

Mental component. After 3 months, both the psychotherapy and paroxetine groups showed improvement compared with treatment as usual ($P = 0.007$). At 1-year follow-up, however, the improvement was similar in all 3 groups.

If Bonferroni corrections are made to adjust the significance levels in Table 4 for the fact that 2 primary and 2 secondary measures have been analyzed at 2 time points each, then the superiority of psychotherapy and paroxetine over usual treatment at 15 months remains significant at $P < 0.008$. However, the remaining differences are no longer significant at the 5% level.

To account for drop-outs, the intention to treat analyses in Table 4 were repeated using the data imputed by SOLAS. The result for days with pain at 3 months was significant at $P < 0.001$ (psychotherapy and paroxetine greater than treatment as usual), as was that for the

SF-36 physical component score at 15 months. The SF-36 mental component score was significant at $P = 0.001$ (psychotherapy and paroxetine greater than treatment as usual) at 3 months, and the SCL global severity was significant at $P = 0.004$ (paroxetine greater than treatment as usual) at 3 months.

Psychological distress as a possible mediating variable. To assess whether improved SF-36 physical component score could be explained in terms of reduced psychological distress, an analysis of covariance was performed. This showed that even after allowing for the effect of age, sex, baseline SF-36 physical component score, and change in SCL-90 global severity score (level of psychological distress), the differences between the psychotherapy, paroxetine, and usual treatment groups on the improvements in SF-36 physical component score at 1 year remained highly significant (adjusted means: 5.53 [SEM, 1.10], 5.00 [SEM, 1.09], and 0.29 [SEM, 1.09], respectively; $P = 0.001$).

Table 4. Abdominal Pain, and SF-36 and SCL-90 Scores in the Psychotherapy, Paroxetine, and Usual Treatment Groups Over 3 Time Periods

	Psychotherapy			Paroxetine			Usual treatment			ANCOVA <i>P</i>
	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n	
Primary outcome measures										
Visual analogue scale for typical pain										
Baseline	67.8	1.81	85	67.6	1.62	86	66.7	1.73	86	
T1	-16.1	3.30	74	-20.6	3.51	74	-11.4	3.08	79	0.17
T2	-15.0	3.55	72	-16.3	3.18	83	-15.6	3.19	77	0.94
SF-36 physical component score										
Baseline	38.2	1.04	82	36.7	1.24	83	38.3	1.24	81	
T1	2.2	0.91	58	2.4	1.33	59	-0.5	0.88	63	0.24
T2	5.2	1.26	59	5.8	1.00	72	-0.3	1.17	61	< 0.001 ^a Psy, Parox > TAU
Secondary outcome measures										
Pain days per month										
Baseline	25.9	0.77	85	22.6	0.99	86	24.0	0.91	83	
T1	-10.1	1.51	57	-8.5	1.70	59	-4.3	1.23	64	0.014 Parox > TAU
T2	-9.9	1.59	60	-5.8	1.61	68	-6.2	1.36	64	0.44
SF-36 mental component score										
Baseline	39.9	1.46	82	41.0	1.36	83	40.6	1.42	81	
T1	5.4	1.68	58	3.7	1.75	59	-0.5	1.60	63	0.007 ^b Psy, Parox > TAU
T2	1.9	1.70	59	2.2	1.55	72	3.8	1.57	61	0.70
Possible mediating variable										
SCL-90 global severity index										
Baseline	0.90	0.07	82	0.96	0.07	86	0.83	0.06	83	
T1	-0.13	0.06	65	-0.24	0.06	67	0.02	0.06	70	0.021 ^c Parox > TAU
T2	-0.12	0.06	68	-0.18	0.06	81	-0.11	0.06	71	0.86

ANCOVA, analysis of covariance; T1, change from baseline to 3 months; T2, change from baseline to 15 months; Psy, psychotherapy; Parox, paroxetine; TAU, usual treatment.

^a*P* < 0.001.

^b*P* < 0.01.

^c*P* < 0.05.

Direct health care costs. *During the treatment period.* The direct health care costs were significantly greater for psychotherapy, but not paroxetine, compared with treatment as usual (Table 5).

During the 1-year follow-up period. The mean annual direct health care costs were significantly lower for psychotherapy (\$976; SD, \$984) compared with treatment as usual (\$1663; SD, \$3177) but not for paroxetine (\$1252; SD, \$1616). This difference was accounted for principally by a reduction in gastroenterologist and other visits, which formed a high proportion of direct health care costs in all 3 groups (Figure 3).

Productivity costs. The cost of days lost from work constituted approximately one third of the total cost and was similar in all groups. During the 15 months of the trial, 10 of 17 patients in the psychotherapy group ceased invalidity benefits compared with 3 of 7 in the paroxetine group and 3 of 11 in the

treatment-as-usual group. By contrast, 3 patients in the psychotherapy group, 9 in the paroxetine group, and 3 in the treatment-as-usual group commenced benefits (Table 6).

A number of one-way and multi-way sensitivity analyses were performed to account for potential variability of costs between different centers. The main cost analyses were repeated using maximum and minimum cost scenarios, including varying the costs by ±50%. Variations in these unit costs did not alter the results of the trial.

Ancillary Analyses

Patients' global rating. After 3 months, the number of patients who recorded an overall improvement in IBS symptoms was 44 of 74 (60%) in the psychotherapy group, 49 of 74 (66%) in the paroxetine group, and 30 of 80 (38%) in the treatment-as-usual group (χ^2 , 14.1;

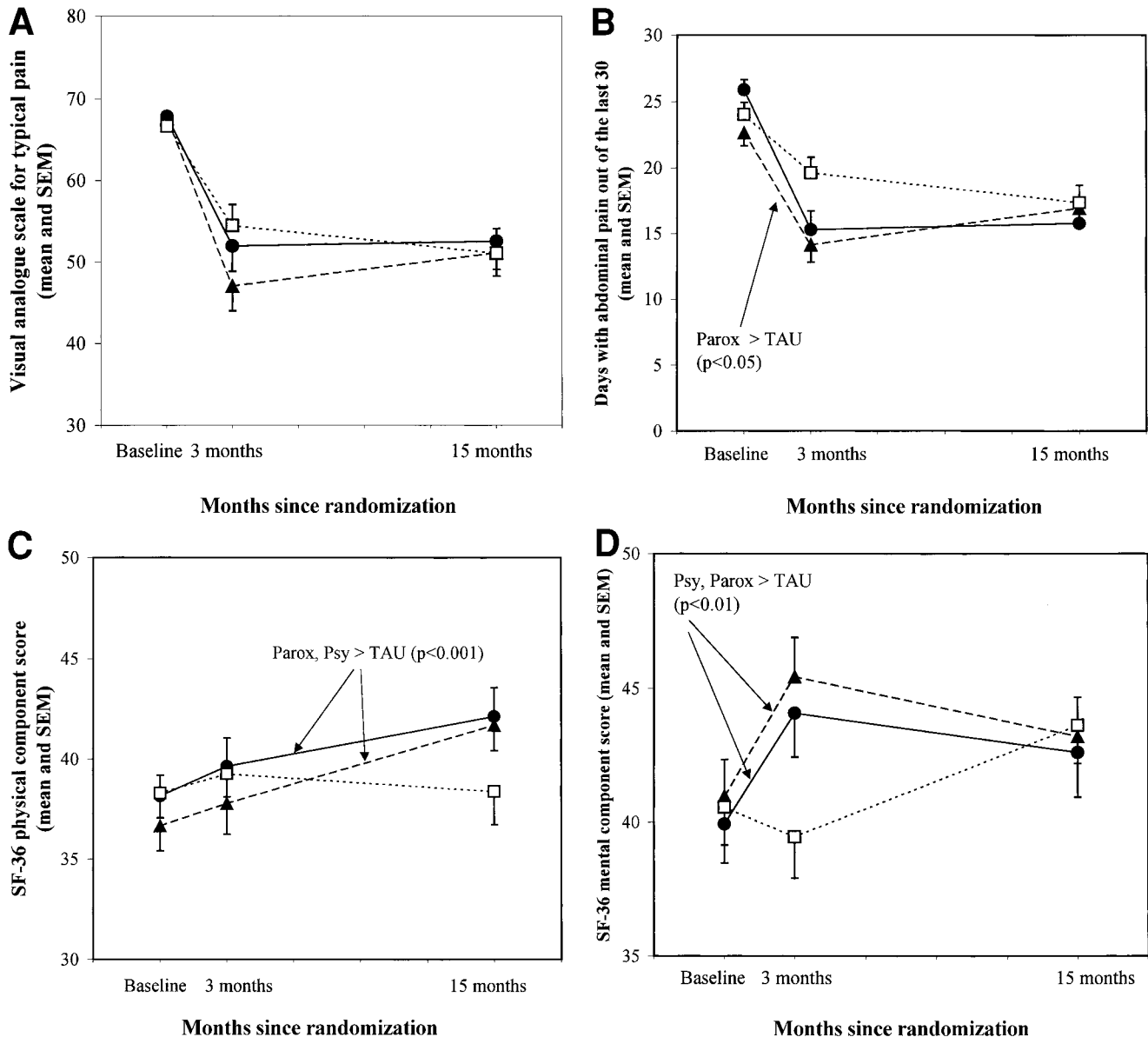


Figure 2. Mean scores for main outcome variables at baseline, 3 months, and follow-up for psychotherapy, paroxetine, and treatment as usual. ●, Psychotherapy; ▲, Paroxetine; □, treatment as usual.

$P = 0.001$). At 1-year follow-up, the proportions were 46 of 74 (62.2%), 48 of 84 (57.1%), and 40 of 78 (51.3%) for the 3 groups, respectively ($\chi^2 = 1.8$; $P = 0.40$).

Rome diagnosis. There were no differences between the subtypes of IBS on any of the primary outcome measures. There were also no differences when the analyses were repeated (1) with men and women analyzed separately or (2) with very severe and severe pain groups analyzed separately, except that the significance levels were reduced because of the small numbers of men and patients with very severe pain.

Outcome and compliance with treatment. In view of the variable compliance with psychotherapy and paroxetine, a secondary, per protocol analysis was performed including only those patients who were fully compliant with treatment (Table 7). At 3 months, patients in the paroxetine group but not those in the psychotherapy group showed significantly more reduction in both severity and frequency of abdominal pain ($P = 0.007$) than the treatment-as-usual group. Both psychotherapy and paroxetine groups improved in the psychological component of health-related quality of life at 3 months. At 1 year,

Table 5. Costs per Week for the 3-Month Treatment Period and the 12-Month Follow-up Period

	Psychotherapy (n = 85)		Paroxetine (n = 86)		Usual treatment (n = 86)		Bias-corrected 95% confidence intervals for intervention against usual treatment	
	Mean	SD	Mean	SD	Mean	SD	Psychotherapy	Paroxetine
Direct health care costs ^a								
Baseline to 3 months	36.67	53.14	29.79	24.82	25.82	37.01	1.41 to 17.60 ^b	-7.29 to 4.54
3 months to 15 months	18.77	18.93	24.08	31.07	31.98	61.10	-9.34 to -0.05 ^b	-6.39 to 4.50
Baseline to 15 months	23.12	16.21	25.38	25.84	30.29	52.10	-5.39 to 2.08	-5.29 to 3.58

NOTE. Costs are in U.S. dollars.

^aDirect health care costs had missing data for 5 patients in the psychotherapy group and 3 in the usual treatment group.

^b*P* < 0.05.

the results were similar to those obtained in the intention-to-treat analysis. When Bonferroni corrections were used to adjust for multiple outcome measures (Table 7), the difference between both active treatments and treatment as usual remained significant at the 5% level for the SF-36 physical component score at 15 months and the mental component score at 3 months.

The numbers of patients receiving a prescription for paroxetine or another SSRI antidepressant during the follow-up year were 16 of 85 (19%) in the psychotherapy group and 19 of 86 (22%) in the treatment-as-usual group; 36 of 86 (42%) in the paroxetine group continued this medication (χ^2 , 13.3; *P* = 0.001). Nine people in the treatment-as-usual group received psychological treatment.

Patients in the paroxetine group who continued antidepressants during the follow-up period did not have more severe symptoms, which could explain this. Patients in the psychotherapy group who took antidepressants during the follow-up year reported significantly less improvement after 3 months of treatment than those who did not take antidepressants (adjusted change score in SF-36 physical component score from baseline to 3 months was -0.7 [SEM, 1.3] for those who did and 4.1 [SEM, 1.1] for those who did not take antidepressants during the follow-up period).

In the psychotherapy group, patients without depressive disorder at baseline improved significantly more

than those with depressive disorder (change in SF-36 physical component score at follow-up, adjusted for age, sex, and baseline SF-36 physical component score: 7.3 [SEM, 1.3] vs. 0.4 [SEM, 2.0]; *P* = 0.007). By contrast, in the paroxetine group, the improvement scores were similar (5.8 [SEM, 1.1] vs. 5.8 [SEM, 1.7]; *P* = 0.98). In the treatment-as-usual group, patients with depressive disorder tended to do worse than the remainder (adjusted SF-36 physical component change score at follow-up, -3.3 [SEM, 2.1] vs. 0.9 [SEM, 1.9]; *P* = 0.11).

Clinical relevance of improvement in health-related quality of life. The SF-36 physical component score and its relationship with ability to work was examined. At the start of the trial, 70 subjects were unemployed due to their illness, 21 were unemployed for other reasons, and 166 were not unemployed (i.e., employed, students, housewives, or retired). A one-way analysis of variance with Bonferroni adjusted pairwise comparisons of these 3 groups showed that the patients who were unemployed due to ill health had significantly lower SF-36 physical component scores (mean, 29.1; SEM, 1.15) than either those who were unemployed for other reasons (mean, 41.4; SEM, 2.12) or those who were not unemployed (mean, 40.9; SEM, 0.73) (*P* < 0.001). The mean of 29.1 is more than 2 SDs below the population norm (mean, 50; SD, 10).

At the end of the follow-up year, data were available regarding the numbers of days missed from work because

Table 6. Number of Patients in Each Group Receiving Invalidation Benefits at the Beginning and End of the Trial

	Psychotherapy	Paroxetine	Treatment as usual
Not on invalidity benefits at any time during trial (%)	50 (71.4)	67 (80.7)	59 (80.8)
Receiving benefits at beginning and end of trial (%)	7 (10)	4 (4.8)	8 (11.06)
Started receiving benefits during trial (%)	3 (4.3)	9 (10.8)	3 (4.1)
Ceased receiving benefits during trial (%)	10 (14.3)	3 (3.6)	3 (4.1)

NOTE. χ^2 = 13.54, *P* = 0.035.

Table 7. Abdominal pain, SF-36, and Psychological Scores in the Psychotherapy, Paroxetine, and Usual Treatment Groups Over 3 Time Periods for Fully Compliant Subjects Only

	Psychotherapy			Paroxetine			Usual treatment			ANCOVA <i>P</i>
	Mean	SEM	n	Mean	SEM	n	Mean	SEM	n	
Primary outcome measures										
Visual analogue scale typical										
Baseline	68.9	2.08	59	67.2	2.37	43	66.7	1.73	86	0.027 ^a Parox > TAU 0.91
T1	-15.9	3.56	57	-24.8	4.65	43	11.4	3.08	79	
T2	-14.8	4.17	52	-15.1	4.77	43	-15.7	3.19	77	
SF-36 physical component score										
Baseline	37.4	1.25	58	36.8	1.89	41	38.3	1.24	81	0.061 0.002 ^b Psy, Parox > TAU
T1	2.6	0.96	47	3.8	1.69	34	-0.5	0.88	63	
T2	5.3	1.47	43	5.6	1.25	39	-0.3	1.17	61	
Secondary outcome measures										
Days with pain in the past 30										
Baseline	26.3	0.87	59	22.3	1.36	43	24.0	0.91	83	0.007 ^b Parox > TAU 0.68
T1	-9.1	1.76	43	-10.0	1.92	36	-4.3	1.23	64	
T2	-9.8	1.94	42	-5.3	2.41	36	-6.2	1.36	64	
SF-36 mental component score										
Baseline	41.6	1.72	58	39.5	2.03	41	40.6	1.42	81	0.001 ^b Psy, Parox > TAU 0.79
T1	4.7	1.91	47	5.8	2.44	34	-0.5	1.60	63	
T2	1.0	1.98	43	4.4	2.18	39	3.8	1.57	61	
Possible mediating variable										
SCL-90 global severity index										
Baseline	0.84	0.08	58	0.96	0.10	43	0.83	0.06	83	0.001 ^b Parox > TAU 0.78
T1	-0.14	0.05	53	-0.31	0.07	43	0.02	0.06	70	
T2	-0.09	0.06	51	-0.19	0.08	43	-0.11	0.06	71	

NOTE. n = 188. Comparisons have been made using ANCOVA to adjust for baseline scores.

T1, change from baseline to 3 months; T2, change from baseline to 15 months. Psy, psychotherapy; Parox, paroxetine; TAU, usual treatment. ANCOVA, analysis of covariance.

^a*P* < 0.01.

^b*P* < 0.05.

of illness for 138 employed patients. Of these, 63 (46%) had missed 7 days or more. An analysis of covariance comparing the change in physical component score from baseline to 15-month follow-up (adjusting for age, sex, initial score, and treatment group) showed that those who missed 7 or more days of work had a significantly smaller improvement than those who missed 6 days or less (adjusted means are 2.3 and 7.2, respectively [SEM, 1.1 and 1.0, respectively]; *P* = 0.002).

Multivariate analysis to determine predictor variables. In the psychotherapy group, 3 variables were identified in the forward stepwise multiple regression analysis explaining 36.1% of the variation in the outcome variable (change in SF-36 physical component score from baseline to 15-month follow-up). In the order they were selected, these were a reported history of sexual abuse, unemployment, and baseline SF-36 physical component score (Table 8). In the paroxetine group, 2 variables were selected (baseline SF-36 physical component score and unemployment). These accounted for 21.4% of the variance.

In the psychotherapy group, after adjusting for baseline SF-36 physical component score and unemployment, the 6 patients with a reported history of sexual abuse recorded an improvement in SF-36 physical component score (adjusted mean, 16.4; SEM, 3.2) compared with those without such a history (adjusted mean, 3.9; SEM, 1.1) (*P* = 0.001; analysis of covariance). In the paroxetine group, the corresponding scores were 9.9 (SEM, 2.3) for the reported sexual abuse group and 5.1 (SEM, 0.9) for the remainder (*P* = 0.066). In the treatment-as-usual group, the corresponding scores were 0.5 (SEM, 3.6) and -0.4 (SEM, 1.3) (*P* = 0.91), respectively (*P* = 0.82).

Summary of Results

Primary outcomes. The psychotherapy and paroxetine groups showed no significant difference from the treatment-as-usual group in terms of reduction in abdominal pain, but both were significantly superior in terms of health-related quality of life (SF-36 physical component score) (first hypothesis).

Table 8. Stepwise Multiple Regression to Predict Change in SF-36 Physical Component Summary Score for Psychotherapy and Paroxetine Group

		For final model				
Step	Variable included	Adjusted R ² (%)	Significance of improvement	Regression coefficient	Standard error	Significance at each level
Psychotherapy group						
	Constant			22.6	4.60	<0.0005
1	Severe sexual abuse	12.9	0.003	12.5	3.42	0.001
2	Unemployed	21.7	0.009	-8.0	2.15	<0.0005
3	Baseline SF-36 physical component score	36.1	<0.0005	-0.4	0.11	<0.0005
Paroxetine group						
	Constant			23.5	3.95	<0.0005
1	Baseline SF-36 physical component score	14.1	0.001	-0.4	2.24	0.008
2	Unemployed	21.4	0.008	-6.1	0.10	<0.0005

Psychotherapy, but not paroxetine, led to a significant reduction in health care costs during the follow-up year compared with usual treatment, but there were no significant differences in costs over the whole trial period (second hypothesis).

Secondary outcomes. The improvement in health-related quality of life observed in the 2 treatment groups could not be explained solely by reduction of psychological distress (SCL-90 score). In the psychotherapy group, patients with a reported history of sexual abuse did better than the remainder and patients with depressive disorder did significantly worse than the remainder. In the paroxetine group, there was no difference between patients with and without depressive disorder (third hypothesis).

Discussion

Interpretation

This study provides, for the first time, information about the cost-effectiveness of psychotherapy and treatment with the SSRI antidepressant, paroxetine, for patients with severe IBS in the United Kingdom. We have confirmed that health care costs are high and quality of life is markedly impaired for patients with severe IBS, with approximately half of the patients having a psychiatric diagnosis. However, the patient sample included in this study was heterogeneous, with one fourth markedly disabled and unemployed through ill health (i.e., drawing sickness benefits) whereas another one fourth missed only the occasional day from work through illness in the 3 months before trial entry. We found that psychother-

apy was acceptable to two thirds of this population, whereas one half accepted paroxetine.

In the intention to treat analysis, we have shown for the first time that the SSRI paroxetine is effective in reducing the number of days of pain in patients with severe IBS, at least in the short-term, which is the time scale used by most efficacy studies. We chose to use an SSRI rather than a tricyclic antidepressant for reasons of compliance.³¹ A recent meta-analysis indicated that no good efficacy studies exist to show the benefit of SSRIs in patients with IBS.⁹ Our results now argue for more clinical trials of their efficacy in patients with IBS.

In the intention-to-treat analysis, both psychotherapy and paroxetine were superior to treatment as usual in providing long-term benefit in quality of life but neither showed a beneficial effect on IBS pain in the long-term. As is usual in effectiveness studies, the findings are less impressive than those reported in smaller short-term efficacy trials using more selected patients; however, our results pertain to psychotherapy and paroxetine in the usual clinical setting, with patients with severe IBS who were refractory to the usual treatments. It appears that even patients in the treatment-as-usual group made some improvement in terms of abdominal pain (Table 4). This may be the natural course of the disorder, even in its severe form, but such improvement must be regarded as quite limited because the changes on other measures were slight. On the visual analogue scale for pain today (data not given above), the mean score for the treatment-as-usual group was reduced by only 3.6 (out of 100) to a mean score of 32.8 at 15 months of follow-up. The number of days per month in pain was reduced from 24

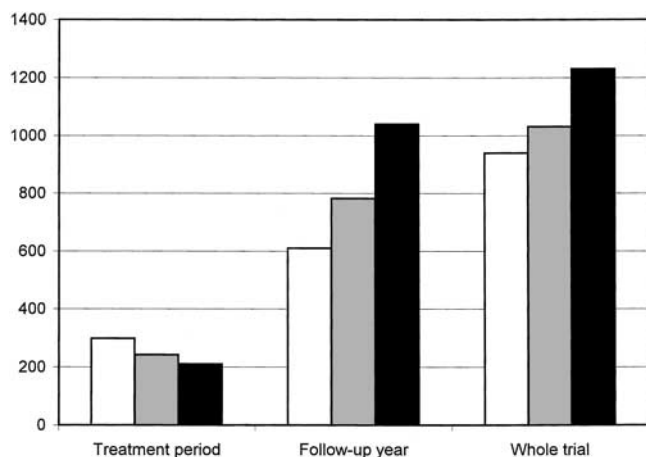


Figure 3. Mean direct health care cost per patient by treatment group for the 13 weeks of the trial, the 52 weeks before follow-up, and 65 weeks for the whole trial. □, Psychotherapy; ■, Antidepressants; ■, usual treatment.

to 17.8 (Table 4). On both of these measures, these patients remained quite ill.⁴

The magnitude of the improvement in SF-36 physical component score after psychotherapy or paroxetine is remarkable. This represents an effect size of 0.61 for psychotherapy and 0.67 for paroxetine. This degree of improvement corresponds to a change in the patient regarding his/her IBS from “severe/very severe” (affecting one’s lifestyle) to “moderate” (cannot be ignored but does not affect your lifestyle).¹⁶ It is also similar to the improvement observed following successful antacid treatment of gastroesophageal reflux disease,³² duodenal ulcer,³³ or coronary revascularization for angina.³⁴

The strengths of this study are its large size, the high proportion of patients available for follow-up 1 year after the end of treatment, and the detailed measurements of abdominal pain and psychological symptoms, health-related quality of life, and costs.¹⁴ The disadvantage of these detailed measurements is the large number of outcome measures. This seems inevitable while the ways of measuring outcome in IBS trials remain unclear,^{15,35} and we would argue that frequency and intensity of pain, health-related quality of life, and costs are all different outcome measures and should be regarded as such.³⁶ However, in view of the large number of outcome measures, the results reported at a marginal level of significance should be treated with caution. We have performed a statistical correction of multiple outcomes, and the principal finding that psychotherapy and paroxetine lead to improvement in the physical component aspects of health-related quality of life remains highly significant.

Psychotherapy incurred additional costs over treatment as usual, but these were offset by reduced costs for the 12 months following treatment. The same trend was found with paroxetine, but the difference from treatment as usual did not reach statistical significance. In addition, psychotherapy, unlike paroxetine, was associated with a small reduction in the number of people claiming invalidity benefits. However, these are preliminary findings and require replication.

Generalizability

There are 3 limitations to the generalizability of the findings of this study to all patients with IBS. First, our results refer only to those patients with severe IBS symptoms. Second, the pragmatic design of the trial necessitated that, although we standardized the interventions, we did not standardize usual care conditions for the following year.¹¹ This meant that patients were able to receive other therapies, including antidepressants, during the follow-up year.³⁷ Interestingly, any “contamination” of the treatments did not obscure the improvement observed in health-related quality of life. Third, the cost data cannot be generalized to countries in which other health care systems operate, and the relative costs of psychotherapeutic and gastroenterological treatment may differ from those in the United Kingdom.

This trial assessed clinical effectiveness rather than efficacy, so we did not include a placebo group. The latter is important to show efficacy, but we had previously assessed the efficacy of this form of psychotherapy⁷ and the efficacy of antidepressants has been shown in a meta-analysis,⁹ although the information regarding SSRI antidepressants was regarded as limited.

The main disadvantage of this type of design is that the researchers have no control over the treatment received by the usual care group; this is particularly important during the 1-year follow-up period. However, the same criticism would pertain to an efficacy trial if a prolonged follow-up was used. We did not ask patients directly why they continued or stopped paroxetine after the 3-month treatment period, but we noted that half (43 of 86) of the patients who were randomized to paroxetine during the 3-month treatment period continued antidepressants throughout the follow-up period. These patients who continued on paroxetine did not have more severe pain or worse health-related quality of life than the remainder. The patients randomized to psychotherapy who took antidepressants during the follow-up period were those who had made the least improvement at 3 months.

The advantages of the usual care group concern the generalizability of the results. Although the efficacy of psychotherapy and antidepressants has been shown in efficacy trials, their effectiveness (i.e., usefulness in the clinical population) has not previously been assessed. One of the main strengths of this study is that we could recruit 81% of a clinic population of patients with severe IBS and show in this population the effectiveness and cost-effectiveness of psychological treatments. Such information is not gained by placebo-controlled trials. Thus, our previous efficacy trial showed psychotherapy to be very efficacious in the patients from a single clinic who were recruited to this treatment and who were compared to a group who had equal time with the therapist but without active psychotherapy.⁷ In the current study, which included a larger and more broadly representative sample of patients with severe IBS unresponsive to usual treatments, we found that psychotherapy was not as efficacious as previously shown but that there are significant advantages over usual care with regard to health-related quality of life and health care costs. We believe this difference is largely due to the different selection of patients; the previous study recruited patients solely from a tertiary referral center, where there is likely to be a higher proportion of patients with abuse and associated psychological problems. In addition, effectiveness trials usually show a less impressive result than efficacy trials. The advantages and limitations of prescribing paroxetine in this population have also been shown in this study. Patients with depressive disorder do better with paroxetine than with psychotherapy. Compliance with paroxetine was only 50%, suggesting that side effects and unwillingness to take an antidepressant are important considerations in this population. These advantages and disadvantages may not have emerged from an efficacy study, which only recruited patients willing to enter a placebo-controlled trial. Thus, the information gained when this type of trial is used is of direct applicability to clinicians working in gastroenterology settings.

Overall Evidence

The improvement in the physical component of health-related quality of life is not simply a reflection of reduced psychological distress, because the results were very similar even after adjustment for this. Health-related quality of life is only partly influenced by symptoms; personal motivation, social support, and overall health perception are also important³⁸ and impairment may be associated with a reported history of sexual abuse even

after controlling for the effects of psychiatric disorder.³³ This may underlie the marked improvement following psychotherapy in patients who reported a history of sexual abuse. This result is based on small numbers and therefore needs to be replicated. It is also notable that the improvement in health-related quality of life occurred during the following year as has been observed with psychological treatment of patients with chronic fatigue syndrome.⁴⁰

At 15-month follow-up, only paroxetine helped patients who had depressive disorder at the start of the trial, whereas the beneficial effect of psychotherapy seems to be independent of its effect on marked depression. This raises the possibility that the 2 treatments act on pain in different ways. The dose of paroxetine (20 mg) may have been too low to adequately treat anxiety or depressive disorders. Further trials are needed to assess whether SSRI antidepressants in effective doses help IBS patients through a direct effect on pain or through resolution of depression.

The improvement in health-related quality of life in the absence of a significant difference in pain severity may reflect the fact that psychological distress in patients with chronic pain is not associated with pain intensity but is strongly associated with the number of pain days and interference with activities.⁴¹ Our previous report, which only reported baseline data of this sample, indicated that both bowel symptoms and psychological distress independently and significantly contribute to impaired health-related quality of life in patients with severe IBS.⁴² The current report indicates that over the follow-up period improvement in health-related quality of life can be achieved even when pain severity does not change greatly.

The psychodynamic interpersonal therapy used in the trial is an evidence-based psychological treatment.¹⁹ It was developed in the United Kingdom but has many similarities with interpersonal therapy, which is well established in the United States. It has been modified for use in general medical settings and has been successfully used with patients with dyspepsia, as well as with IBS. The therapists are trained to open a conversational style of interview that is not threatening or difficult for the patient. This requires a long first session, but we believe this is why the therapy has been acceptable to most of our patients, even those who would not usually be regarded as suitable for psychotherapy (i.e., patients do not have to be psychologically minded). The early parts of treatment concentrate on the patients' symptoms, for which help is being sought, and later goes on to explore psychological

issues. The therapy may not be widely available so the choice between psychotherapy or antidepressant treatment will depend upon availability of psychotherapy and/or patient choice.

In conclusion, treatment of patients with severe IBS should include, treatment with either psychotherapy or a suitable antidepressant as these reduce the limitations on daily life imposed by the disorder (physical component of health-related quality of life) at no additional cost. Further studies are needed to clarify which patients respond or do not respond to each treatment, or a combination of both, and to elucidate the underlying mechanisms in those in whom such treatments are effective.

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