Review

Treatment of irritable bowel syndrome: a review of randomised controlled trials

Summary
Irritable bowel syndrome (IBS) is a common chronic disorder that is associated with significant disability and health care costs. The purpose of this paper is to review and assess published randomised controlled trials examining the clinical effectiveness of interventions for IBS for 1987–1998. A literature search was conducted to identify randomised controlled trials of IBS treatments: 45 studies were identified that described randomised controlled trials and of these, six fulfilled all three criteria used to assess the quality of randomised controlled trials, as described by Jadad and colleagues.[1] These criteria are: adequate description of randomisation, double blinding, and description of withdrawals and dropouts. It is concluded that there are few studies which offer convincing evidence of effectiveness in treating the IBS symptom complex. This review strongly suggests that future work should include well designed trials that: describe the randomisation method; use internationally approved diagnostic criteria; and are double blinded and placebo controlled. Clear well defined outcome measures are necessary. Inclusion of quality of life measures allows comparison between trials in different therapeutic areas. Conducting such studies will help to overcome some of the difficulties identified in this review.

Introduction

IBS is the most common functional bowel disorder and affects about 20% of all people at any one time.[2 3] It is a condition characterised by abdominal pain associated with defecation, or a change in bowel habit and with features of disordered defecation and distension in the absence of any demonstrable abnormality.[2] Three subgroups exist: one third of patients suffer constipation, one third suffer diarrhoea, and the rest suffer alternating constipation and diarrhoea.[3 4] While patients with symptoms of IBS represent 20–50% of referrals to gastroenterologists, there are many who do not seek medical attention.[5]

The burden of illness associated with IBS is considerable. One recent study in the UK[6] found IBS sufferers to report substantially lower quality of life scores, as measured by the SF36, than the control group. Sufferers also used health service resources to a greater extent and missed more days off work than the control group.

A number of pharmaceutical companies have new drugs in development to treat IBS and there is interest in the use of psychotherapy, either alone or in conjunction with other therapy. Before these therapies are adopted it is important to assess the evidence on the effectiveness of what is already available. It is highly likely that in the very near future a crop of new efficacy studies will be published.

This paper therefore reviews the quality and direction of current evidence.

Methods

LITERATURE SEARCH

To identify the studies used in this review, the following databases were searched: Cochrane Library, Database of Abstracts of Reviews of Effectiveness (DARE), Medline, and Embase. The key words "colonic diseases", "functional", and "clinical trials" were used. General reviews, meta-analyses, and references from published randomised controlled trials (RCTs) were also used. Trials published between 1987 and 1998 in English, French, German, Italian, and Spanish were included.

INCLUSION CRITERIA

In order to be included in this review, a study had to have been published in a peer reviewed journal and to be judged by the authors of this review to be truly randomised. RCTs dealing with bulking agents, anticholinergics/antispasmodics, antidiarrhoeals, prokinetic drugs, antidepressants including psychotropic drugs, serotonergic antagonist drugs, combinations of drugs, as well as recent and miscellaneous drugs were included. Trials comparing different treatments without placebo control groups were also included. High fibre diet or a fibre supplementation taken in all randomised groups was also included.

EXCLUSION CRITERIA

Trials published as abstracts or letters, or not clearly randomised were excluded. RCTs which analysed drugs with only a pharmacological effect on motility were also excluded.

ASSESSMENT OF RCTS

In the RCTs identified, the following points were assessed:

- sample size
- number of dropouts
- extent to which blinding was used
- intervention
- outcome measures such as global assessment of symptoms by the patient or physician, abdominal pain, constipation, diarrhoea, or abdominal distension.

Results

A total of 227 studies were identified between 1987 and 1998. There was some duplication of the studies identified from the various databases. Of these 227 studies, 93 described trials. Only 45 trials were used in this review as the remaining 48 were either not randomised or studies of gut motility. The interventions described included: bulking agents, anticholinergics/antispamodics, antidiarrhoeals, serotonergic drugs, antidepressants/psychotropic drugs, prokinetic drugs, as well as recent and miscellaneous drugs. These 45 studies are outlined in table 1.

The quality of these 45 trials was assessed according to the simple criteria laid down by Jadad and colleagues[1]: whether the method of randomisation was described; whether the study was double blinded; and whether a description of withdrawals and dropouts from the study was included. It is possible that these studies used appropriate methods of randomisation but failed to describe them. Other more complicated critical appraisal checklists are available.[52] However, it was felt that very few

Abbreviations used in this paper: IBS, irritable bowel syndrome; RCT, randomised controlled trial

Table 1 Summary of randomised controlled trials (RCTs) of irritable bowel syndrome: clinical effectiveness studies

Study	*Treatments compared*	*Diagnostic criteria*	*Study design*	*Patients entered*	*No of dropouts*	*Treatment period*	*Outcome measures*	*Result*
Bulking agents								
Cook *et al*, 1990 (Canada)[7]	4 cookies (20 mg corn fibre)	Manning	DB, XO	n=14	n=5	12 weeks each with a 4 week washout period	Pain frequency, severity, and duration; stool frequency and consistency, additional symptoms	No difference was found between corn fibre and placebo but both were effective in alleviating overall symptoms.
	Placebo							
Jalihal and Kurian, 1990 (India)[8]	Ispaghula husk 30 g/day	Symptoms of IBS	DB, XO	n=22	n=2	4 weeks each with 1 week or 10 day washout period	Overall well being, individual symptoms, transit time	Ispaghula therapy resulted in improvement in overall symptoms and satisfying bowel movements (p<0.001) but produced no change in abdominal pain or flatulence.
	Placebo							
Lucey *et al*, 1987 (UK)[9]	12 bran biscuits (1=1.3 g fibre)	Manning	DB, XO	n=44	n=16	3 months each	Pain score, bowel score, general score, total symptom score	Improvement after the treatment compared with pretreatment in both the bran treated (p<0.01) and placebo treated groups (p<0.01). No significant difference between bran therapy or placebo.
	12 placebo biscuits (1=0.23 g fibre)							
Prior and Whorwell, 1987 (UK)[10]	Ispaghula husk (1 sachet of Regulan tid containing 3.6 g refined active mucilloid 56% ispaghula)	3 symptoms	DB	n=80 (total)	n=8	12 weeks	Global assessment, bowel habit, transit time, abdominal pain, bloating	Overall assessment was improved in 82% of patients receiving ispaghula and 53% of the placebo group (p<0.02) Constipation was improved significantly (p<0.02) as well as decreased transit time (p<0.001) in those with high transit time.
	Placebo				n=15			
Snook and Sheperd, 1994 (UK)[11]	Bran fibre (12 g/day)	Rome	DB, XO	n=80	n=9	7 weeks each with a 2 week washout period	Overall symptom improvement, abdominal pain, bloating, wind, bowel habit disturbance	Overall symptomatic improvement in 52% patients with bran and in 54% with placebo. Also, bran supplementation was no more effective than placebo for wind related symptoms.
	Placebo							
Toskes *et al*, 1993 (Argentina)[12]	Calcium polycarbophil 6 g/day (twelve 0.5 g tablets)	1 symptom	DB, XO	n=28	n=5	6 months	Global evaluation, ease of passage, bloating, nausea, pain	Polycarbophyll was rated better than placebo for relief of bloating, nausea, and pain, but was not statistically significant. Significant difference was found for ease of passage (p<0.05).
	Placebo							
Tomas Ridocci *et al*, 1992 Spain)[13]	Plantago ovata	Symptoms of IBS	DB	n=10	None	1 month	Frequency and consistency of stools, transit time, flatulence	Significant increase in frequency of stools as well as decrease in consistency of stools was found compared with placebo. Also, increase in faecal weight and decrease in transit time was found.
	Placebo			n=10	None			
Antispasmodic/ anticholinergic (AS/ACH) drugs								
Awad *et al*, 1995 (Mexico)[1]	Pinaverium bromide 50 mg tid	Rome	DB	n=20	n=1	3 weeks	Pain duration, frequency, severity and distension, stool frequency, consistency, additional symptoms	Significantly decreased pain duration and abdominal distension compared with placebo (p<0.01).
	Placebo			n=20	n=1			
Baldi *et al*, 1992 (Italy)[15]	Octylonium bromide 40 mg tid	1 symptom	DB	n=35	n=1	4 weeks	Abdominal pain, bloating, bowel movement frequency	Significantly reduced pain and bloating, and increased the pain threshold (p<0.02) compared with placebo. Also, reduced sigmoid motility during distension (p<0.05) compared with placebo.
	Placebo			n=37	None			

Table 1 Continued

Study	Treatments compared	Diagnostic criteria	Study design	Patients entered	No of dropouts	Treatment period	Outcome measures	Result
Centonze *et al*, 1988 (Italy)[16]	Cimetropium bromide 50 mg tid	1 symptom or more	DB, parallel group	n=24	n=1	6 months	Intensity and frequency of pain, days with bowel disturbances, patient and psychological assessments, adverse reactions	Significantly reduced pain ($p<0.01$), improved overall symptoms ($p<0.01$) compared with placebo. However, 48% patients had side effects (mainly dry mouth and sleepiness).
	Placebo			n=24	n=3			
Dobrilla *et al*, 1990 (Italy)[17]	Cimetropium bromide (CB) 50 mg/tid	2 symptoms	DB, parallel group	n=70 (total)	None	3 months	Frequency and severity of pain, distension, evidence of contracted colon, overall patient assessment	Significantly reduced pain ($p<0.0005$) as well as number of pain episodes ($p<0.001$) compared with placebo. Six patients taking CB complained of dry mouth.
	Placebo				n=1			
Lawson *et al*, 1988 (Australia)[18]	Peppermint oil 0.2–0.4 ml tid	Symptoms of IBS	DB, XO	n=25	None	4 weeks	Abdominal pain, bloating, stool frequency and consistency, urgency, incomplete evacuation, global severity, side effects	No significant difference between the treated and placebo groups in symptom score and global assessment of symptoms.
	Placebo							
Lech *et al*. 1988 (Netherlands)[19]	Peppermint oil 200 mg tid	3 symptoms	DB	n=19	n=4	4 weeks	Symptoms, side effects	Peppermint oil improved symptoms in 68% patients compared with 22% in the placebo group ($p<0.02$). The main side effect was pyrosis with a peppermint taste.
	Placebo			n=23	n=1			
Liu *et al*, 1997 (Taiwan)[20]	Colpermin 187 mg tid/qid	Symptoms of IBS	DB	n=110 (total) n=52*	n=3	4 weeks	Pain, distension, frequency, borborygmi, flatulence	Peppermint oil improved symptoms in 78% of patients, and was significantly more effective than placebo ($p<0.05$).
	Placebo			n=49*	n=6			
Mollica and Manno, 1992 (Italy)[21]	Octylonium bromide 20 mg tid + diazepam 2 mg tid	Symptoms of IBS	DB	n=30 (total)	None	3 weeks	Type and frequency of stools, pain, bloating, anxiety	Both treatments reduced GI symptoms even though OB alone was not effective. The combined drug reduced anxiety, and produced no side effects.
	Octylonium bromide 20 mg tid				None			
Passaretti *et al*, 1989 (Italy)[22]	Cimetropium bromide (CB) 50 mg tid	Symptoms of IBS	DB, parallel group	n=40 (total)	n=4	1 month	Transit time, constipation, abdominal pain, global improvement, side effects, symptom scores	CB shortened the gut transit time ($p<0.01$) in patients with prolonged transit time as well as improved the global clinical condition ($p<0.03$) compared with placebo. The drug was effective in a subgroup of IBS patients with constipation.
	Placebo				n=3			
Schafer and Ewe, 1990 (Germany)[23]	Hyoscine-*N*-butyl-bromide (Buscopan) (30 mg/day) plus paracetamol 1500 mg/day	Symptoms of IBS	DB, parallel group	n=177	n=14	4 weeks	Symptoms including abdominal pain measured on an analogue scale	Overall improvement was found in 81% of the patients in buscopan plus group, 76% in the buscopan group, 72% in the paracetamol group, and 64% in the placebo group. Significant difference was found between the buscopan plus and the placebo ($p<0.0001$), and the buscopan group and the placebo ($p<0.001$). 5% of the patients experienced adverse effects.
	Buscopan 30 mg/day			n=182	n=14			
	Paracetamol 1500 mg/day			n=175	n=14			
	Placebo			n=178	n=8			
Shaw *et al*, 1991 (UK)[24]	Peppermint	Symptoms of IBS	Open, parallel groups	n=17	None	6 months	Abdominal pain, flatulence, distension, stool consistency, constipation, frequency and severity of symptoms	3/17 on peppermint oil and 13/18 in the stress management group reported overall benefit.
	Stress management group			n=18	None			

Table 1 Continued

Study	*Treatments compared*	*Diagnostic criteria*	*Study design*	*Patients entered*	*No of dropouts*	*Treatment period*	*Outcome measures*	*Result*
Van Outryve *et al*, 1995 (Belgium)[25]	Mebeverine (MB) plain capsules 135 mg 2tid	1 symptom or more	DB, XO	n=60	n=2	6 weeks each	Patient and investigator assessment of improvement in pain, bloating, flatulence, constipation, alternating stool pattern and frequency	Both MB plain and MB SR capsule were significantly effective in more than 80% of patients. MB SR provided equivalent efficacy and tolerance to MB plain in the treatment.
	Mebeverine sustained release (SR) 200 mg bid			n=111 (total)				
Combination of drugs with bulking agents								
Chapman *et al*, 1998 (UK)[26]	Mebeverine 135 mg tid + high fibre dietary advice	1 symptom	Open, parallel group	n=111 (total) n=49*	n=8	8 weeks	Severity and frequency of pain, bowel frequency, stool consistency, side effects	Both treatment groups showed significant improvements in the number of pain attacks and their severity. 28% of the mebeverine/ispaghula group found their treatment unpalatable.
	Mebeverine 135 mg tid + 3.5 g ispaghula husk bid/tid			n=54*				
Misra *et al*, 1989 (India)[27]	Ispaghula husk 10 g/day + propantheline 15 mg tid (B)†	Manning	Open	n=28 (total) n=11*	n=1	6 months	Incomplete evacuation, pain, constipation, straining, diarrhoea, mucous, total symptom score	The overall relapse rate in group B was 46% compared with 82% in group A. Patients in group B became significantly asymptomatic from the 4th month ($p<0.05$–0.01) while patients in group A continued to deteriorate. In part II study, the relapsed patients who were treated 6/7 became asymptomatic within four weeks.
	Placebo (A)			n=13*	n=3			
Nayak *et al*, 1997 (India)[28]	Placebo	Manning	Open	n=15	None	60 days	Pain frequency, severity and duration, stool frequency and consistency, mucous, incomplete evacuation, additional symptoms, total symptom score, propagated contractions in rectosigmoid	Improvement in frequency and duration of pain, and mucus in stool was better with MND than with placebo ($p<0.001$ for both). ISP improved all symptoms except stool consistency ($p<0.05$) better than placebo, and was better than MND in improving severity of pain, mucus in the stool and complete evacuation ($p<0.05$).
	Metronidazole (MND) 400 mg tid for 10 days followed by placebo for 60 days			n=15	None			
	Ispaghula 10 g bid (ISP)			n=15	None			
Villagrasa *et al*, 1991 (Spain)[29]	Diet with high roughage (20 g of fibres) and 10 g of bran	Symptoms of IBS	Open	n=53	Not given	24 months	Pain, distension	OB significantly reduced abdominal pain and distension ($p<0.01$) after 12 months compared with before treatment. High fibre diet did not show significant improvement. OB seems to be more effective than a high fibre diet ($p<0.01$).
	Octylonium bromide (OB) 40 mg tid and normal diet (10–15 g of fibre)			n=61	Not given			
Antidepressants|psychotropic drugs								
Alevizos *et al*, 1989 (Greece)[30]	Amineptine 200 mg/day	Rome and Hamilton depression score	DB	n=20	n=3	6 weeks	Hamilton depression scale score, Langner's 22 item score, Zung depression and Zung anxiety scale scores	Amineptine improved the total Hamilton-D score compared with placebo ($p<0.004$), and was more effective on depressed mood, retardation, and cognitive dysfunction.
	Placebo			n=20	n=1			

Table 1 Continued

Study	*Treatments compared*	*Diagnostic criteria*	*Study design*	*Patients entered*	*No of dropouts*	*Treatment period*	*Outcome measures*	*Result*
Barbier *et al*, 1989 (France)[31]	Buzepide metiodide 3 mg + haloperidol 0.3 mg tid	Symptoms of IBS	DB	n=224 (total)	n=1	2 months	Abdominal pain, distension, global assessment score, visual scale	Significantly reduced frequency as well as intensity of abdominal pain ($p< 0.05$) and distension ($p<0.05$) compared with placebo.
	Placebo				n=5			
Greenbaum *et al*, 1987 (USA)[32]	Desipramine	2 symptoms or more	DB, XO	n=41 (total)	n=12	A four week observation period preceded three 6 week test periods	Number of stools, loose stools, pain index, self reported diarrhoea and constipation, brief psychiatric assessment, Hamilton depression rating scale, rectosigmoid manometry, retrospective global assessment	Desipramine decreased stool frequency, diarrhoea, abdominal pain, and depression significantly in diarrhoea predominant patients compared with atropine and placebo ($p<0.025$ for both).
	Atropine				None			
	Placebo				n=2			
Tanum and Malt, 1996 (Norway)[33]	Mianserin 120 mg/day	1 symptom	DB	n=49 (total) n=25*	n=2	7 weeks	Observer completed ratings, global improvement scale, patient self ratings, visual analogue scale, disability scales	Reduced symptoms of abdominal pain, distress, and functional disability compared with placebo ($p<0.001$).
	Placebo			n=22*	None			
Serotonergic antagonist drugs								
Goldberg *et al*, 1996 (UK)[34]	Ondansetron 16 mg tid	1 symptom or more	DB, XO	n=12	n=3	2 weeks each with a 2 week washout period	Pain, distension, stool consistency, straining, general well being, rectal sensitivity tests,	Significantly decreased distension and frequency of abdominal pain ($p<0.03$ for both) compared with placebo, and caused firmer bowels ($p<0.01$) in all subjects.
	Placebo							
Maxton *et al*, 1996 (UK)[35]	Ondansetron (OD) 4 mg tid	Rome	DB, XO	n=50	n=1	4 weeks each with a 2 week washout period	Pain, distension, nausea, heartburn, postprandial discomfort, flatulence, lethargy, back pain, bowel habits, urinary symptoms, hospital anxiety and depression scale	Reduced bowel frequency ($p<0.035$) and improved stool consistency ($p<0.002$) in diarrhoea predominant IBS as well as functional dyspepsia ($p<0.02$) compared with placebo. No significant improvement was seen for abdominal pain or distension.
	Placebo							
Steadman *et al*, 1992 (USA)[36]	Ondansetron hydrochloride* 16 mg tid	Manning	DB, XO	n=14	n=11	4 weeks each with a 4 week washout period	Colonic transit, small intestinal and orocecal transit, responses of peptide hormones, stool consistency, pain	Colonic transit tended to be longer but this was not significant. On the whole, the drug was no better than placebo.
	Placebo							
Prokinetic drugs								
Farup *et al*, 1998 (Norway)[37]	Cisapride 5 /10 (DD) mg tid**	Rome	DB, parallel group	n=33 (n=17 DD)	n=5	12 weeks	Global symptom rating, pain, frequency and consistency of stool, difficulty of passage, need to defecate, incomplete evacuation, bloating, general well being	No significant differences were found between cisapride and placebo group. The trial seems to exclude the possibility that 15–30 mg cisapride daily has a clinically significant effect in patients with C-IBS.
	Placebo			n=37 (n=23 DD)	n=3			

Table 1 Continued

Study	*Treatments compared*	*Diagnostic criteria*	*Study design*	*Patients entered*	*No of dropouts*	*Treatment period*	*Outcome measures*	*Result*
Schutze *et al*, 1997 (Austria)[38]	Cisapride 5 mg tid**	Rome	DB	n=48	n=6	12 weeks	Investigators assessment: pain, constipation, bloating, other symptoms, nervousness, anxiety, tenseness, depression patient's assessment: visual analogue scale	No difference was found between cisapride and placebo group. However, cisapride improved stool passage from pretreatment condition ($p<0.05$). It may be of benefit in C-IBS.
	Placebo			n=48	n=4			
Van Outyrve *et al*, 1991 (Belgium)[39]	Cisapride 5 mg tid**	Symptoms of IBS	DB	n=36	n=4	12 weeks	Stool frequency and consistency, pain, distension, flatulence, visual analogue scale	Reduced severity and frequency scores of abdominal pain and flatulence ($p<0.05$ for both) than placebo. Response to treatment was good or excellent at week 12.
	Placebo			n=33	n=5			
Antidiarrhoeal drugs								
Efskind *et al*, 1996 (Norway)[40]	Loperamide 2 mg/day	2 symptoms or more	DB, parallel group	n=90 (n=35)*	n=21	5 weeks	Stool frequency and consistency, pain, visual analogue scale	Reduced stool frequency ($p<0.001$), improved stool consistency ($p<0.01$) and reduced intensity of pain ($p<0.03$) compared with placebo but increased pain in the night, so drug should be given in divided doses.
	Placebo Healthy controls			n=34* n=33				
Halpern *et al*, 1996 (USA)[41]	Lacteol Forte 2 capsules bid	Symptoms of IBS	DB, XO	n=29	n=11	6 weeks each with a 2 week washout period	Pain, bloating, frequency and consistency of stools, mucous, general physical state, daily mean index	Overall significantly improved six clinical criteria in 50% of patients compared with placebo ($p<0.018$).
	Placebo							
Hovdenak, 1987 (Norway)[42]	Loperamide 4 mg nocte	Symptoms of IBS	DB, parallel group	n=30	n=1	3 weeks	Diarrhoea, alternating bowel habits with and without pain, constipation	Improved stool frequency and consistency as well as overall symptoms compared to placebo ($p<0.01$ for both). The drug can be considered for some IBS patients who has painless diarrhoea or alternating bowel habits with abdominal pain.
	Placebo			n=30	n=1			
Lavo *et al*, 1987 (Norway)[43]	Loperamide 2/4 mg/day***	1 symptom	DB	n=11*	n=1	13 weeks	Stool consistency and frequency, urgency, pain, flatulence and borborygmi, adverse effects	Improved stool consistency ($p<0.001$), abdominal pain ($p<0.02$) urgency ($p<0.05$) as well as overall response ($p<0.03$) compared with placebo. Self titration of dose and a single nightly dose is safe and efficient.
	Placebo			n=10*	n=2			
Lunardi *et al.* 1991 (Italy)[45]	Sodium cromoglycate 500 mg qid	2 symptoms or more	DB, XO	n=2	n=2	8 weeks each with a 4 week washout period	Symptom score card	Mean symptom score improved with the treatment of sodium cromoglycate compared with placebo ($p<0.003$). The drug seems to be useful in IBS patients with food intolerance.
	Placebo			n=18				
Prior *et al*, 1988 (UK)[45]	Lidamidine hydrochloride 8/16 mg/day	3 symptoms	DB, XO	n=72	n=15	4 weeks each with a 2 week washout period	Frequency and severity of pain, distension, heartburn, nausea, postprandial discomfort, frequency of bowel movements, global assessment	Reduced frequency of defecation compared with placebo ($p<0.005$) but no effect on abdominal pain.
	Placebo			n=57				

Table 1 Continued

Study	*Treatments compared*	*Diagnostic criteria*	*Study design*	*Patients entered*	*No of dropouts*	*Treatment period*	*Outcome measures*	*Result*
Rodriguez-Magallan *et al*, 1997 (Mexico)[46]	Lidamidine	Manning	DB, XO	n=10	None	6 weeks each with a 2 week washout period	Global response,	Overall response was better with lidamidine than placebo ($p<0.02$). No significant differences were found with or without psychotherapy.
	Placebo			n=10	None			
	Lidamidine + psychotherapy			n=10	n=1			
	Placebo + psychotherapy			n=10	n=1			
New and miscellaneous drugs								
Cann *et al*, 1994 (UK and Italy)[47]	Loxiglumide 200 mg tid	2 symptoms	DB, parallel group, pilot study	n=24	None	8 weeks	Pain, distension, change in bowel habit, patient and physician's overall assessment	400 mg tid induced significant improvement (63%) in overall IBS symptoms compared with 200 mg tid (57%) and placebo (48%).
	Loxiglumide 400 mg tid			n=23	None			
	Placebo			n=25	None			
Dapoigny *et al*, 1995 (France)[48]	Fedotozine 3.5 mg tid	2 symptoms or more	DB	n=56	n=10	6 weeks	Maximal pain scores, bloating, changes in bowel function, stool consistency and frequency, overall patient evaluation	30 mg dose was superior to placebo in relieving maximal abdominal pain ($p=0.01$), mean daily pain ($p<0.007$), abdominal bloating ($p<0.02$), and overall disease severity ($p<0.003$).
	Fedotozine 15 mg tid			n=57	n=7			
	Fedotozine 30 mg tid			n=63	n=6			
	Placebo			n=62	n=11			
Gade and Thorn, 1989 (Denmark)[49]	Paraghurt tablets	Symptoms of IBS	DB	n=32	None	4 weeks	Physicians overall assessment, constipation, diarrhoea, abdominal pain, meteorism, borborygmi, flatulence	Overall assessment was significantly improved compared with placebo ($p<0.002$).
	Placebo			n=22	None			
Mathais *et al*, 1994 (USA)[50]	Leuprolide acetate (Lupron depot 3.75 mg /month	Symptoms of IBS	DB	n=14*	n=1	3 months	Nausea, vomiting, bloating, pain, anorexia, early satiety, overall visit score, total symptom score, overall evaluations by patient and investigator, hydrogen breath and Sitzmarks tests	Progressively improved nausea, vomiting, bloating, abdominal pain and early satiety, and overall symptoms than placebo ($p<0.01$–0.05). All hormone levels decreased ($p<0.05$) except luteinizing hormone.
	Placebo			n=15*	n=1			
Mathais *et al*, 1994 (USA)[51]	Leuprolide acetate (Lupron depot 1.0–1.5 mg/day); plus oestrogen replacement	Symptoms of IBS	DB	n=28 (total)	None	9 months (3 months to 12 months)	Individual symptom scores including: nausea, pain, bloating, vomiting, anorexia, early satiety, total symptom scores, overall and global assessment scores	Longer period of treatments had more striking and significant changes in all the symptoms of IBS.
	Placebo				None			

DB, double blind; XO, crossover; DD, double dose.
*No of patients who completed the study; **constipation predominant patients; ***diarrhoea predominant patients.
†Patients had become completely asymptomatic for 4–6 weeks before entering the study .

Table 2 Quality assessment of irritable bowel syndrome randomised controlled trials

Study	Randomisation method	Double blind	Description of withdrawals and dropouts
Alevizos *et al*, 1989[30]	Random numbers	Yes	Yes
Awad *et al*, 1995[14]	No method described	Yes	Yes
Baldi *et al*, 1992[15]	No method described	Yes	Yes
Barbier *et al*, 1989[31]	Drawing lots	Yes	Yes
Cann *et al*, 1994[47]	No method described	Yes	Yes
Centonze *et al*, 1988[16]	No method described	Yes	Yes
Chapman *et al*, 1990[26]	No method described	No	Yes
Cook *et al*, 1990[7]	No method described	Yes	Yes
Dapoigny *et al*, 1995[48]	No method described	Yes	Yes
Dobrilla *et al*, 1990[17]	Consecutive outpatients	Yes	Yes
Efskind *et al*, 1996[40]	No method described	Yes	Yes
Farup *et al*, 1998[37]	No method described	Yes	Yes
Gade and Thorn, 1989[49]	No method described	Yes	Yes
Greenbaum *et al*, 1987[32]	No method described	Yes	Yes
Goldberg *et al*, 1996[34]	No method described	Yes	Yes
Halpern *et al*, 1996[41]	No method described	Yes	Yes
Hovdenak, 1987[42]	No method described	Yes	Yes
Jalihal and Kurian, 1990[8]	No method described	Yes	Yes
Lavo *et al*, 1987[43]	No method described	Yes	Yes
Lawson *et al*, 1988[18]	No method described	Yes	Yes
Lech *et al*, 1988[19]	No method described	Yes	Yes
Liu *et al*, 1997[20]	No method described	Yes	Yes
Lucey *et al*, 1987[9]	No method described	Yes	Yes
Lunardi *et al*, 1991[44]	No method described	Yes	Yes
Mathias *et al*, 1994a[50]	No method described	Yes	Yes
Mathias *et al*, 1994b[51]	No method described	Yes	Yes
Maxton *et al*, 1996[35]	No method described	Yes	Yes
Misra *et al*, 1989[27]	Consecutive patients	No	Yes
Mollica and Mano, 1992[21]	No method described	Yes	Yes
Nayak *et al*, 1997[28]	No method described	Yes	Yes
Passaretti *et al*, 1989[22]	Consecutive outpatients	Yes	Yes
Prior and Whorwell, 1987[10]	Consecutive patients	Yes	Yes
Prior *et al*, 1988[45]	No method described	Yes	Yes
Rodriguez-Magallan *et al*, 1997[46]	No method described	Yes	Yes
Schafer and Ewe, 1990[23]	No method described	Yes	Yes
Shaw *et al*, 1991[24]	No method described	No	Yes
Schutze *et al*, 1997[38]	No method described	Yes	Yes
Snook and Sheperd, 1994[11]	Consecutive patients	Yes	Yes
Steadman *et al*, 1992[36]	No method described	Yes	Yes
Tanum and Malt, 1996[33]	No method described	Yes	Yes
Tomas Ridocci *et al*, 1992[13]	No method described	Yes	Yes
Toskes *et al*, 1993[12]	No method described	Yes	Yes
Van Outyrve *et al*, 1991[39]	No method described	Yes	Yes
Van Outryve *et al*, 1995[25]	No method described	Yes	Yes
Villagrasa *et al*, 1991[29]	No method described	No	No

trials would have been included in a more rigorous list of criteria. Table 2 summarises the characteristics of the 45 trials to which the Jadad criteria were applied.

When applying the criteria, only six of the RCTs identified provided adequate information,[10 11 17 22 30 31] highlighting the lack of well designed and well reported trials of IBS. Of the six studies meeting the criteria, two were of bulking agents,[10 11] two were of antispasmodic or anticholinergic drugs,[17 22] and two were of antidepressant/psychotropic drugs.[30 31] The fact that only six studies met even such a relatively minimal set of criteria suggests that the quality of the current evidence is not good. Because so few studies met the criteria, further discussion has not been confined to them but has embraced all 45 studies listed in table 2.

BULKING AGENTS

Seven double blind, placebo controlled trials of bulking agents are listed in table 1. The study carried out by Snook and Shepherd[11] of 80 patients in a double blind, crossover trial not only found bran supplementation to be no more effective than placebo in improving individual symptoms of IBS but for wind related symptoms it was significantly less effective. Prior and Whorwell[10] examined a total of 80 patients and found significant differences in bowel habit and transit time in those with constipation and in overall well being between the groups receiving ispaghula husk and placebo.

The appears to be some evidence that bulking agents may be effective in treating constipation associated with IBS although there is little reason to believe that they are effective for the entire IBS symptom complex.

ANTISPASMODICS/ANTICHOLINERGIC DRUGS

Twelve trials of antispasmodics (most of which were anticholinergics) were identified. Passaretti and colleagues[22] carried out a study on 40 patients who were given cimetropium bromide (50 mg three times daily) or placebo for one month and found that the antispasmodic significantly ($p<0.01$) shortened whole gut transit time in patients with prolonged transit time. It also improved the global clinical condition compared with placebo ($p=0.029$). These findings were further supported by Dobrilla and colleagues[17] in a three month study. In this study of 70 consecutive outpatients, cimetropium bromide (50 mg three times daily) was found to significantly reduce pain as well as the number of pain episodes compared with placebo at the end of three months ($p<0.001$). Moreover, 89% of patients treated with cimetropium considered themselves to be globally improved compared with 69% in the placebo group ($p=0.039$).

ANTIDEPRESSANT/PSYCHOTROPIC DRUGS

In general, antidepressants are used for patients with persistent painful symptoms with or without associated psychiatric morbidity. It has been suggested that the tricyclic antidepressants may have a beneficial effect in IBS mediated via a mechanism other than their antidepressant activity.[53] Four trials of antidepressants were reported. Alevizos and colleagues[30] described a study comparing the antidepressant amineptine 200 mg/day with placebo for six weeks in 40 patients who satisfied the criteria for IBS and scored at least 15 in the 24 item Hamilton depression scale (HAM-D). The study found that amineptine produced significantly greater improvement for the total Hamilton score than patients who received placebo at the end of the trial period. Amineptine was more effective in treating depressed mood, retardation, and cognitive dysfunction. Barbier and colleagues[31] studied the efficacy and safety of a combination of buzepide metiotide and haloperidol for two months in 224 patients. This combination resulted in improvement in frequency of symptoms and intensity of the most frequent symptoms, abdominal pain and distension, compared with placebo. Patients receiving the drug combination also reported greater global improvement than the placebo group.

Discussion

DIAGNOSTIC CRITERIA (ENTRY CRITERIA) USED IN TRIALS

A major consideration in the design of a treatment trial is characterisation of the entity to be studied as this will determine the nature of the patients who are enrolled. Unless physiological markers are found, the diagnosis of IBS is usually made on the basis of clinical history (the presence of abdominal pain, abdominal distension, and a disordered bowel habit) and exclusion of organic disease. Criteria outlined by Manning and colleagues[54] help to diagnose the condition more positively, thus allowing studies on the disorder to be more comparable. The more recently defined "Rome criteria"[55] provide an international consensus on diagnosis and adequate entry criteria for a clinical trial in IBS. Of the 47 trials identified, six used Manning criteria,[54] six used Rome criteria,[55] and the remaining 35 trials used either symptoms of IBS, or defined one, two, or three symptoms of IBS as entry criteria.

Classification into diarrhoea predominant and constipation predominant categories appears to reflect physiological differences between each type.[56] For studies on prokinetic drugs,[37–39] entry criteria required patients to have constipation predominant symptoms. However, of seven antidiarrhoeal trials only one used the presence of diarrhoea predominant IBS as an entry criterion.

It is recommended that patients meet clear standardised entry criteria to be included in trials. Talley and colleagues[57] recommend the use of the Rome criteria. The authors also recommend that limiting trials to defined subgroups of patients should be considered to enhance homogeneity of the study population.

STUDY DESIGN

Considerations that are especially relevant to the design of controlled treatment trials for IBS are the use of placebo control, study duration, baseline comparisons, maintaining blindedness, and the appropriateness of the commonly used crossover design. There were a number of common problems with the studies identified. A major problem with designing RCTs for the treatment of IBS is the placebo response, which is extremely variable and high, most frequently between 40% and 70%.[58] This was a particular problem in three studies reported in table 1.[7 9 11] Differences of this magnitude reflect not only the nature of the patients enrolled in a trial but the methods used to determine treatment response. It is impossible to be certain that even marked improvements are due to the intrinsic properties of the treatment being tested unless there is a placebo control group. Therefore, it is recommended that all IBS trials be placebo controlled.[57 58]

All of the trials included clearly mentioned the number of patients given either treatment or placebo. One study provided incomplete information concerning the number of dropouts[40] and one study failed to mention the number of dropouts.[29]

RANDOMISATION

All of the 45 studies were considered to be RCTs yet only seven mentioned the method of randomisation.[10 11 17 22 27 30 31] The other 40 trials may have been appropriately randomised yet failed to describe the method of randomisation. It is considered important not only to describe the method of randomisation but also to provide information regarding the frequency of a variety of characteristics in the treatment and control groups to ensure adequate similarity between the two groups.[57]

BLINDING

Forty one of 47 RCTs were double blinded. None of the four studies[26–29] on combinations of drugs with bulking agents or high fibre diet were blinded. This was expected as it would be difficult to achieve blinding in such studies. No blinding was possible in the study of Shaw and colleagues[24] in which peppermint oil treatment was compared with a stress management programme. Talley and colleagues[57] recommend that all IBS trials are double blinded. Where this is not possible such as in non-drugs trials of treatments such as psychotherapy, it is essential that independent evaluators are used to rate the effectiveness of treatment.

TREATMENT PERIOD (DURATION OF TRIALS)

IBS is usually a chronic, sometimes lifelong, condition with unpredictable periods of exacerbation and remission. Thus clinical trials of only a few days or weeks are of limited relevance for establishing that a treatment is effective. As can be seen from table 1, the majority of IBS treatment trials were of insufficient duration to be clinically relevant. The studies that fulfilled the Jadad criteria[1] reported treatment periods varying from one month[22] to six months.[27] In all 45 trials, the duration of the treatment period is clearly mentioned together with any washout period in the crossover trials. It is recommended that trials of IBS treatments be a minimum of 8–12 weeks' duration.[57] Maxton and colleagues[59] suggest a total trial duration of approximately 12 weeks.

OUTCOME MEASURES

Because there are no objective markers in improvement of IBS, determination of efficacy in treatment trials is based on somewhat arbitrary rating scales. A change in abdominal pain, bowel habit, and overall well being are the main outcome measures used in IBS trials, with distension tending to be neglected, although patients often perceive it as severe.[58] The studies reported here used a range of outcome measures, including nausea, vomiting, abdominal pain (frequency, severity, and duration), bowel habit (frequency, consistency of stools, and transit time), distension, and overall symptom scores, as assessed by the patient or physician. Specific measures were also used, appropriate to the therapeutic agent. For example, in a tricyclic antidepressant study, a standard measure of depression (Hamilton-D score) was used as it was anticipated that a significant proportion of enrolled patients would be depressed.[30] Northcutt and colleagues[60] used adequate pain relief as an outcome measure in their study of alosteron, a 5-HT_3 receptor antagonist. In a review, Talley and colleagues[57] strongly proposed the need to develop sensitive symptom outcome measures as a priority among their recommendations to optimise IBS trials. The authors recommended that symptom outcome measures should include multiple domains and that quality of life should be assessed in addition to gastrointestinal symptoms. They also suggest that global assessment scales are useful although further research is needed to determine the degree to which global well being and health or symptoms are correlated. If resources to expand the treatment of IBS are to be found, future studies will need to include generic quality of life measures to allow comparison with effects in completely different therapeutic areas.

REVIEWS OF IBS TREATMENTS

No Cochrane review of IBS treatments was identified in this review. However, other reviews have highlighted the flaws in IBS study design. For example, Pace and colleagues,[61] in a review of fibre supplementation, found the studies to be flawed due to high placebo response, small sample size, short duration of treatment, inadequate dose or mode of fibre delivery, and ill defined inclusion criteria. The authors also found that in the five antidepressant studies reviewed, all had methodological and statistical problems.

A recent meta-analysis by Pittler and Ernst[62] reported that the role of peppermint oil in the symptomatic treatment of IBS has not been established and carefully executed studies are needed to clarify the issue. In a review of anticholinergics, all eight studies were judged to be flawed and with conflicting results.[61] A meta-analysis of 26 selected double blind, randomised trials was performed by Poynard and colleagues[63] which included eight drugs: cimetropium bromide, dicyclomine hydrochloride, mebeverine, hyoscine butyl bromide, octylonium bromide, peppermint oil, pinaverium bromide, and trimebutine. Only five drugs (cimetropium bromide, mebeverine, octylonium bromide, pinaverium bromide, and trimebutine) have been shown to be clinically effective in patients with IBS without adverse reactions.

Conclusions

IBS is a challenging disorder that affects many individuals, and its treatment is extremely complex. A variety of processes appear to be at work and IBS sufferers are not a homogeneous population. Therefore, not all treatments will be suitable for all IBS patients. Rather, certain interventions will be effective towards specific aspects of IBS.

The literature review of treatments for IBS identified few RCTs and a poor overall quality of research. The majority of published trials failed to meet even simple criteria for acceptability. Despite this, a variety of interventions have been shown to be clinically effective in the treatment of symptoms of IBS, although no drug is effective in treating all symptoms. A variety of outcome measures have been used, making it difficult to compare the results of trials.

Several new drugs are currently being developed which show promise in the treatment of IBS.[64] It is essential that RCTs are conducted of consistently identified patients with clearly defined outcome measures. These outcome measures should not only deal with symptom relief but also improvement in quality of life and associated measures such as time off work.

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1 Jadad AR, Moore RA, Caroll D, *et al.* Assessing the quality of reports of randomised clinical trials: is blinding necessary? *Controlled Clin Trials* 1996;**17**:1–12.
2 Thompson WG, Creed F, Drossman DA, *et al.* Functional bowel disease and functional abdominal pain. *Gastroenterol Int* 1992;**5**:75–91.
3 Camilleri M, Choi MG. Review article: irritable bowel syndrome. *Aliment Pharmacol Ther* 1997;**11**:3–15.
4 Malcolm A, Kellow JE. Irritable bowel syndrome: what it is and what to do about it. *Modern Med* 1998;**15**:74–86.
5 Farthing MJG. Irritable bowel, irritable body or irritable brain. *BMJ* 1995; **310**:171–5.
6 Akehurst RL. *Burden of illness of irritable bowel syndrome*. An interim report on behalf of Novartis Pharma AG, Basel, Switzerland. Sheffield: ScHARR, University of Sheffield, 1999.
7 Cook IJ, Irvine EJ, Campbell D, *et al.* Effect of dietary fibre on symptoms of rectosigmoid motility in patients with irritable bowel syndrome. A controlled cross-over study. *Gastroenterology* 1990;**98**:66–72.
8 Jalihal A, Kurian G. Ispaghula therapy in irritable bowel syndrome: improvement in overall well-being is related to reduction in bowel dissatisfaction. *J Gastroenterol Hepatol* 1990;**5**:517–13.
9 Lucey MR, Clark ML, Lowndes J, *et al.* Is bran efficacious in irritable bowel syndrome? A double-blind placebo controlled crossover study. *Gut* 1987;**28**:221–5.
10 Prior A, Whorwell PJ. Double blind study of ispaghula in irritable bowel syndrome. *Gut* 1987;**28**:1510–13.
11 Snook J, Shepherd HA. Bran supplementation in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 1994;**8**:511–14.
12 Toskes PP, Connery KL, Ritchey TW. Calcium polycarbophil compared with placebo in irritable bowel syndrome. *Aliment Pharmacol Ther* 1993;**7**: 87–92.
13 Tomas Ridocci M, Anon R, Minguez M, *et al.* The efficacy of plantago ovata as a regulator of intestinal transit. A double-blind study compared to placebo. *Rev Esp Enferm Dig* 1992;**82**:17–22.
14 Awad R, Dibildox M, Ortiz F. Irritable bowel syndrome using pinaverium bromide as a calcium blocker. A randomised double-blind placebo-controlled trial. *Acta Gastroenterol Latinoam* 1995;**25**:137–44.
15 Baldi F, Longanesi A, Blasi A, *et al.* Octylonium bromide in the treatment of the irritable bowel syndrome: a clinical functional study. *Hepatogastroenterology* 1992;**39**:392–5.
16 Centonze V, Imbimbo BP, Campanozzi F, *et al.* Oral cimetropium bromide, a new muscarinic drug, for long-term treatment of irritable bowel syndrome. *Am J Gastroenterol* 1988;**83**:1262–6.
17 Dobrilla G, Imbimbo BP, Piazzi L, *et al.* Long term treatment of irritable bowel syndrome with cimetropium bromide: a double blind placebo-controlled trial. *Gut* 1990;**31**:355–8.
18 Lawson MJ, Knight RE, Tran K, *et al.* Failure of enteric-coated peppermint oil in the irritable bowel syndrome: A randomised, double-blind cross-over study. *J Gastroenterol Hepatol* 1988;**3**:235–8.
19 Lech AY, Olesen KM, Hey H, *et al.* Behandling af colon irritabile med pebermynteolie. *Ugeskr Laeger* 1988;**150**:2388–9.
20 Liu JH, Chen GH, Yeh HZ, *et al.* Enteric-coated peppermint-oil capsules in the treatment of irritable bowel syndrome: A prospective, randomised trial. *J Gastroenterol* 1997;**32**:765–8.
21 Mollica G, Manno G. Otilonium bromide-diazepam in the treatment of the irritable colon. A controlled study versus otilonium bromide. *Clin Ther* 1992;**141**:129–34.
22 Passaretti S, Guslandi M, Imbimbo BP, *et al.* Effects of cimetropium bromide on gastrointestinal transit time in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 1989;**3**:267–76.
23 Schafer E, Ewe K. The treatment of irritable colon. Efficacy and tolerance of buscopan plus, buscopan, paracetamol and placebo in ambulatory patients with irritable bowel colon. *Fortschr Med* 1990;**108**:488–92.
24 Shaw G, Srivastava ED, Sadlier M, *et al.* Stress management for irritable bowel syndrome: a controlled trial. *Digestion* 1991;**50**:36–42.
25 Van Outryve M, Mayeur S, Meeus MA, *et al.* A double-blind crossover comparison study of the safety and efficacy of mebeverine and mebeverine sustained release in the treatment of irritable bowel syndrome. *J Clin Pharm Ther* 1995;**20**:277–82.
26 Chapman ND, Grillage MG, Mazumder R, *et al.* A comparison of mebeverine with high-fibre dietary advice and mebeverine plus ispaghula in the treatment of irritable bowel syndrome: an open prospectively randomised parallel group study. *Br J Clin Pract* 1990;**44**:461–6.
27 Misra SP, Thorat VK, Sachdev GK, *et al.* Long-term treatment of irritable bowel syndrome: results of a randomised controlled trial. *Q J Med* 1989;**73**:931–9.
28 Nayak AK, Karnad DR, Abrahaam P, *et al.* Metronidazole relieves symptoms in irritable bowel syndrome: the confusion with so-called 'chronic amebiasis'. *Ind J Gastroenterol* 1997;**16**:137–9.
29 Villagrasa M, Boix J, Humbert P, *et al.* Aleatory clinical study comparing otilonium bromide with a fibre-rich diet in the treatment of irritable bowel syndrome. *Ital J Gastroenterol* 1991;**23**:67–70.
30 Alevizos B, Christodoulou GN, Loannidis C, *et al.* The efficacy of amineptine in the treatment of depressive patients with irritable bowel syndrome. *Clin Neuropharmacol Supplement* 1989;**2**:S66–76.
31 Barbier JP, Dorf G, Gordin J, *et al.* Effect of a buzepide metiodide-haloperidol combination in treating functional intestinal disorders. Randomised double-blind controlled versus placebo study. *Ann Gastroenterol Hepatol Paris* 1989;**3**:123–8.
32 Greenbaum DS, Mayle JS, Vanegeren LE, *et al.* Effects of desipramine on irritable bowel syndrome compared with atropine and placebo. *Dig Dis Sci* 1987;**32**:257–66.
33 Tanum L, Malt UF. A new pharmacological treatment of functional gastrointestinal disorder. A double-blind placebo-controlled with mianserin. *Scand J Gastroenterol* 1996;**31**:318–25.
34 Goldberg PA, Kamm MA, Setti CP, *et al.* Modification of visceral sensitivity and pain in irritable bowel syndrome by 5-HT3 antagonism (ondansetron). *Digestion* 1996;**57**:478–93.
35 Maxton DG, Morris J, Whorwell PJ. Selective 5-hydroxytryptamine antagonism: a role in irritable bowel syndrome and functional dyspepsia? *Aliment Pharmacol Ther* 1996;**10**:595–9.
36 Steadman CJ, Talley NJ, Phillips SF, *et al.* Selective 5-hydroxytryptamine type 3 receptor antagonism with ondansetron as treatment for diarrhoea-predominant irritable bowel syndrome: a pilot study. *Mayo Clin Proc* 1992; **67**:732–8.
37 Farup PG, Hovdenak N, Wettterhus S, *et al.* The symptomatic effect of cisapride in patients with irritable bowel syndrome and constipation. *Scand J Gastroenterol* 1998;**33**:128–31.
38 Schutze K, Brandstatter G, Dragoisics B, *et al.* Double-blind study of the effect of cisapride on constipation and abdominal discomfort as components of the irritable bowel syndrome. *Aliment Pharmacol Ther* 1997; **11**:387–94.
39 Van Outryve M, Milo R, Touissaint J, *et al.* 'Prokinetic' treatment of constipation-predominant irritable bowel syndrome: A placebo-controlled study of cisapride. *J Clin Gastroenterol* 1991;**13**:49–57.
40 Efskind PS, Bernklev T, Vatn MH. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. *Scand J Gastroenterol* 1996;**31**:463–8.
41 Halpern GM, Prindiville T, Blankenburg M, *et al.* Treatment of irritable bowel syndrome with Lacteol Fort: a randomised, double-blind, cross-over trial. *Am J Gastroenterol* 1996;**91**:1579–85.
42 Hovdenak N. Loperamide treatment of the irritable bowel syndrome. *Scand J Gastroenterol Suppl* 1987;**130**:81–4.
43 Lavo B, Stenstam M, Nielsen AL. Loperamide in treatment of irritable bowel syndrome: a double-blind placebo controlled study. *Scand J Gastroenterol Suppl* 1987;**130**:77–80.
44 Lunardi C, Bambara LM, Biasi D, *et al.* Double-blind cross-over trial of oral sodium cromoglycate in patients with irritable bowel syndrome due to food intolerance. *Clin Exp Allergy* 1991;**21**:569–72.
45 Prior A, Wilson KM, Whorwell PJ. Double-blind study of an alpha 2 agonist in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 1988; **2**:535–9.
46 Rodnitz-Magallan A, Valadez-Velazquez T, Llorens-Torres F, *et al.* Treatment of irritable colon with lidamidine and support psychotherapy. *Rev Gastroenterol Mex* 1997;**62**:7–13.
47 Cann PA, Rovati LC, Smart HL, *et al.* Loxiglumide, a CCK-A antagonist, in irritable bowel syndrome. A pilot multicenter clinical study. *Ann N Y Acad Sci* 1994;**713**:449–50.
48 Dapoigny M, Abitboll JL, Fraitag B. Efficacy of peripheral kappa agonist fedotozine versus placebo in treatment of irritable bowel syndrome. A multicenter-dose response study. *Dig Dis Sci* 1995;**40**:2244–8.
49 Gade J, Thorn P. Paraghurt for patients with irritable bowel syndrome. A controlled clinical investigation from general practice. *Scand J Prim Health Care* 1989;**7**:23–6.
50 Mathias JR, Clench MF, Reeves Darby VG, *et al.* Effect of leuprolide acetate in patients with moderate to severe functional bowel disease. Double-blind placebo-controlled study. *Dig Dis Sci* 1994;**39**:1155–62.
51 Mathias JR, Clench MH, Roberts PH, *et al.* Effect of leuprolide acetate in patients with functional bowel disease. Long-term follow-up after double-blind placebo-controlled study. *Dig Dis Sci* 1994;**39**:1163–70.
52 Moher D, Jadad AR, Nicol G, *et al.* Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials* 1995;**16**:62–73.
53 Clouse RE. Antidepressants for functional intestinal syndromes. *Dig Dis Sci* 1994;**39**:2352–63.
54 Manning AP, Thompson WG, Heaton KW, *et al.* Towards positive diagnosis of the irritable bowel. *BMJ* 1978;**2**:653–4.

55 Thompson WG, Dotevall G, Drossman D, *et al.* Irritable bowel syndrome: guidelines for the diagnosis. Report of the Rome Working Team. *Gastroenterol Int* 1989;**2**:92–5.
56 Prior A, Maxton DG, Whorwell PJ. Anorectal manometry in irritable bowel syndrome: differences between diarrhoea and constipation predominant subjects. *Gut* 1990;**31**:452–62.
57 Talley NJ, Nyren O, Drossman DA, *et al.* The irritable bowel syndrome: toward optimal design of controlled treatment trials. *Gastroenterol Int* 1993; **6**:189–211.
58 Maxton DG, Morris JA, Whorwell PJ. Ranking of symptoms by patients with the irritable bowel syndrome. *BMJ* 1989;**299**:1138.
59 Maxton DG, Morris J, Whorwell PJ. Improving clinical trials in irritable bowel syndrome: some practical aspects. *Eur J Gastroenterol Hepatol* 1992;**4**:337–41.
60 Northcutt AR, Camilleri M, Mayer EA, *et al.* Alosteron, a $5HT_3$ receptor antagonist, is effective in the treatment of female irritable bowel syndrome. *Gastroenterology* 1998;**114**:A812.
61 Pace F, Coremans G, Dapoigny M, *et al.* Therapy of irritable bowel syndrome. An overview. *Digestion* 1995;**56**:433–42.
62 Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: A critical review and metaanalysis. *Am J Gastroenterol* 1998;**93**:1131–5.
63 Poynard T, Naveau S, Mory B, *et al.* Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Alim Pharmacol Ther* 1994;**8**:499–510.
64 Morgan Stanley Dean Witter. *An investor's primer to irritable bowel syndrome (IBS)*. European Investment Research, 2 June 1999.