

Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome

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SUMMARY

Background: Both high-fibre dietary advice and the prescription of fibre as a bulking agent are very common in primary and secondary care management of irritable bowel syndrome. Irritable bowel syndrome patients with constipation may have delayed intestinal transit. Therefore, fibres that accelerate intestinal transit may be beneficial in these patients. The uncertain benefits reported in several clinical studies, however, have led us to reappraise the value of fibre in irritable bowel syndrome management.

Aim: To quantify the effect of different types of fibre on global and symptom relief from irritable bowel syndrome.

Methods: Using a structured literature search in MEDLINE (1966–2002), we selected randomized controlled trials involving irritable bowel syndrome patients treated with fibre. Analyses were performed for the total group and for trials using soluble and insoluble fibre separately.

Results: Seventeen studies were included in the analysis. None investigated primary care irritable bowel syndrome patients. Fibre, in general, was effective in the relief of global irritable bowel syndrome symptoms

[relative risk, 1.33; 95% confidence interval (CI), 1.19–1.50]. Irritable bowel syndrome patients with constipation may receive benefit from fibre treatment (relative risk, 1.56; 95% CI, 1.21–2.02), but there was no evidence that fibre was effective in the relief of abdominal pain in irritable bowel syndrome. Soluble and insoluble fibre, separately, had different effects on global irritable bowel syndrome symptoms. Soluble fibre (psyllium, ispaghula, calcium polycarbophil) showed significant improvement (relative risk, 1.55; 95% CI, 1.35–1.78), whereas insoluble fibre (corn, wheat bran), in some cases, worsened the clinical outcome, but there was no significant difference compared with placebo (relative risk, 0.89; 95% CI, 0.72–1.11).

Conclusions: The benefits of fibre in the treatment of irritable bowel syndrome are marginal for global irritable bowel syndrome symptom improvement and irritable bowel syndrome-related constipation. Soluble and insoluble fibres have different effects on global irritable bowel syndrome symptoms. Indeed, in some cases, insoluble fibres may worsen the clinical outcome. Future clinical studies evaluating the effect and tolerability of fibre therapy are needed in primary care.

INTRODUCTION

Irritable bowel syndrome is a functional gastrointestinal disorder characterized by recurrent episodes of abdom-

inal pain/discomfort and disturbed bowel habit.¹ It is very common in both primary and secondary care.^{2–4} The aetiology of irritable bowel syndrome is unknown; however, many patients consider dietary factors to play a central role and often modify their diet and/or use additional fibre before consulting their doctor.^{5, 6} Irritable bowel syndrome patients consulting their primary care doctor often receive dietary advice, are

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referred to a dietician or receive a prescription for fibre. Moreover, the addition of over-the-counter wheat bran to the daily meal is an almost universal recommendation in the treatment of irritable bowel syndrome.^{4, 5} Indeed, advice to increase the fibre content of the diet is given to 20–36% of all primary care irritable bowel syndrome patients. In 16%, primary care physicians prescribe ‘pharmacological’ fibres, such as psyllium.^{7, 8}

For our study, we characterized fibres as soluble (psyllium, ispaghula, calcium polycarbophil) and insoluble (corn fibre, wheat bran). Soluble fibre dissolves in water, forming a gel, and is fermented in the colon by bacteria to a greater extent than insoluble fibre. Short-chain fatty acids and gas are the active metabolites of soluble fibre, both of which decrease the gut transit time. This shortened transit time may alleviate constipation and decrease intracolonic pressure, possibly resulting in a reduction in pain. In contrast, insoluble fibre undergoes minimal change in the digestive tract and shortens colonic transit, causing an increase in the faecal mass. Fibres that influence intestinal transit may be beneficial for irritable bowel syndrome patients.^{9–11} Others have suggested that bran, in fact, may worsen irritable bowel syndrome symptoms.^{12, 13}

Systematic reviews have shown that the treatment of irritable bowel syndrome patients with fibre remains controversial.^{14–18} Some studies have reported global irritable bowel syndrome symptoms, whereas others have discussed irritable bowel syndrome-related symptoms, but none has analysed the results for soluble and insoluble fibre separately. In the present meta-analysis, therefore, the aim was to quantify the effectiveness of different types of fibre measured by different outcome measures.

METHODS

Search strategy

A systematic literature search was performed using the MEDLINE database for the period 1966–2002. Search parameters included the medical subject heading terms: ‘functional colonic diseases’, ‘dietary fibre’ and ‘randomized controlled trial’. The free text terms ‘irritable bowel syndrome’, ‘diet therapy’ and ‘trial’ were also used. Furthermore, the reference sections of all articles of interest were reviewed. The search was restricted to articles published in the English language.

Inclusion and exclusion criteria

All randomized controlled trials with a randomized or quasi-randomized allocation of intervention were considered to be eligible for analysis. We concentrated on the following outcome measures: the proportion of patients reporting clinical relief (global irritable bowel syndrome symptom improvement); the proportion of patients reporting improved irritable bowel syndrome-related abdominal pain; and the proportion of patients reporting an improvement in irritable bowel syndrome-related constipation. Studies including a combination of fibre and drug treatment in one of the trial arms were excluded.

Data collection and analysis

Pre- and post-treatment effects with regard to global and symptom improvement were extracted from each study. If necessary, they were recalculated from the original data. The results of individual studies were compiled into The Cochrane Collaboration *Review Manager* and analysed using Metaview 4.1.¹⁹ Relative risks were estimated. The pooled relative risks were estimated with 95% confidence intervals (95% CI) using a fixed-effect model. Heterogeneity between studies was explored using the chi-squared test. If the effect size estimates varied to a greater extent than on the basis of chance alone, a random-effect model was used. The improvement of irritable bowel syndrome symptoms using fibre treatment was considered to be significantly better than control when the lower limit of the 95% CI was greater than unity. Fibre treatment was considered to significantly worsen irritable bowel syndrome symptoms when the upper limit of the 95% CI was less than unity. Analyses were performed for the total group and for trials using soluble and insoluble fibre separately.

RESULTS

Trials identified

Of the 35 studies found, 20 were considered to be potentially relevant for analysis. The main reasons for excluding the selected articles were that the intervention group was not compared with a control group ($n = 6$) and dietary interventions were evaluated in combination with drug therapy ($n = 3$) or combined with other dietary therapies (e.g. elimination diets) ($n = 6$). Three primarily eligible studies were excluded

from the analysis because they reported data from which a relative risk could not be calculated.^{20–22} This left us with 17 studies for the meta-analysis, involving a total of 1363 irritable bowel syndrome patients. Nine studies examined the use of soluble fibres (psyllium, ispaghula, polycarbophil),^{23–31} and eight concentrated on the effectiveness of insoluble fibres (corn fibre, wheat bran).^{32–39} None of the studies included primary care irritable bowel syndrome patients. Table 1 summarizes the specifications of all the included studies.

Efficacy of fibres

Twelve trials reported an improvement in global irritable bowel syndrome symptoms. The pooled relative risk was 1.33 (95% CI, 1.19–1.50) (Figure 1). Fibre treatment was successful in more than half (60%) of the irritable bowel syndrome patients. There was no evidence that fibre was effective in irritable bowel

syndrome patients with abdominal pain (Figure 2). Indeed, in some irritable bowel syndrome patients, fibre may worsen the clinical outcome (relative risk, 0.78; 95% CI, 0.64–0.95). The pooled effect of fibre treatment on irritable bowel syndrome-related constipation was more favourable than placebo (relative risk, 1.56; 95% CI, 1.21–2.02) (Figure 3).

Efficacy of soluble fibre

Of the seven studies of ispaghula,^{23–25, 27–30} six found treatment favourable compared with placebo. Irritable bowel syndrome symptoms were not improved by psyllium therapy.²⁶ Calcium polycarbophil showed relief of global irritable bowel syndrome symptoms and ease of stool passage. There was no significant improvement in either abdominal pain or bloating.³¹ The combination of a high-fibre diet and ispaghula was no better than a combination of a high-fibre diet and

Table 1. Studies included in the meta-analysis and their specifications

Study	Year	Treatment	Dose (per day)	Study design	Duration (weeks)	Outcome measure
Soluble fibre						
Arthurs and Fielding ²³	1983	Ispaghula	2 sachets	DB	4	Global irritable bowel syndrome symptoms
Golechha <i>et al.</i> ²⁴	1982	Ispaghula	NA	DB	3	Abdominal pain
Jalihai and Kurian ²⁵	1999	Ispaghula	30 g	DB	4	Global irritable bowel syndrome symptoms, abdominal pain, constipation
Longstreth <i>et al.</i> ²⁶	1981	Psyllium	6.4 g	DB	8	Global irritable bowel syndrome symptoms, abdominal pain, constipation
Nigam <i>et al.</i> ²⁷	1984	Ispaghula	NA	DB	NA	Global irritable bowel syndrome symptoms
Prior and Whorwell ²⁸	1987	Ispaghula	1 sachet*	DB	12	Global irritable bowel syndrome symptoms, abdominal pain, constipation
Ritchie and Truelove ³⁰	1979	Ispaghula	1 sachet*	DB	12	Global irritable bowel syndrome symptoms
Ritchie and Truelove ³¹	1980	Ispaghula	1 sachet*	DB	12	Global irritable bowel syndrome symptoms
Toskes <i>et al.</i> ²⁹	1993	Calcium polycarbophil	6 g	DB	12	Global irritable bowel syndrome symptoms
Insoluble fibre						
Cann <i>et al.</i> ³²	1984	Wheat bran	10–30 g	DB	9	Abdominal pain, constipation
Cook <i>et al.</i> ³³	1990	Corn fibre	20 g	DB	12	Global irritable bowel syndrome symptoms
Fowle <i>et al.</i> ³⁴	1992	Wheat bran	4.1 g	DB	12	Global irritable bowel syndrome symptoms, abdominal pain, constipation
Kruis <i>et al.</i> ³⁵	1986	Wheat bran	15 g	DB	16	Abdominal pain, constipation
Manning <i>et al.</i> ³⁶	1977	Wheat bran + high-fibre diet	20 g	SB	6	Abdominal pain, constipation
Snook and Shepherd ³⁷	1994	Wheat bran	36 g	DB	7	Global irritable bowel syndrome symptoms
Soltsoft <i>et al.</i> ³⁸	1976	Miller bran	30 g	DB	6	Global irritable bowel syndrome symptoms
Villigrasa <i>et al.</i> ³⁹	1991	Wheat bran + high-fibre diet	20 + 10 g	O	52	Abdominal pain, constipation

DB, double-blind trial; NA, not applicable; O, open trial; SB, single-blind trial.

* Authors postulate that a single sachet may be approximately 5 g.

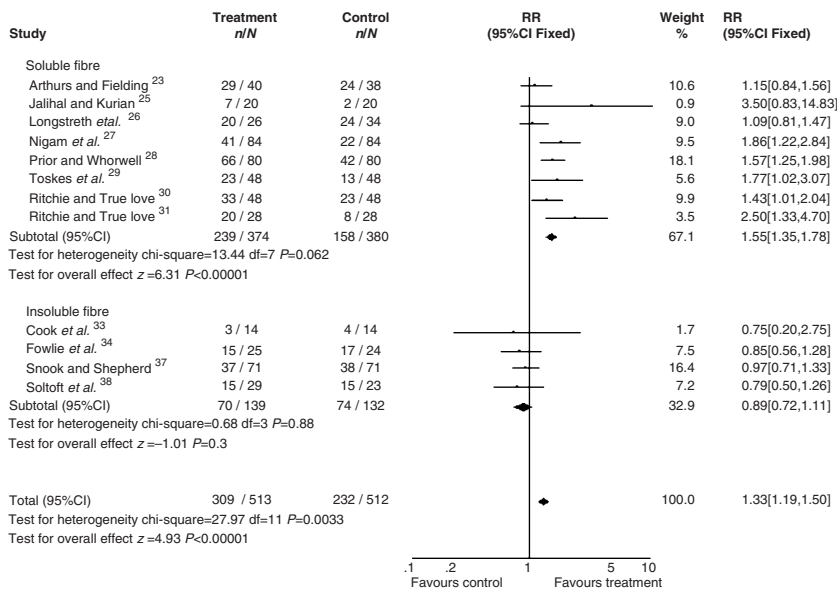


Figure 1. Comparison of different types of fibre and control treatment on global irritable bowel syndrome symptom improvement.

n:number of events in treatment or control group; N: number of participants in treatment or control group; RR: relativrisk

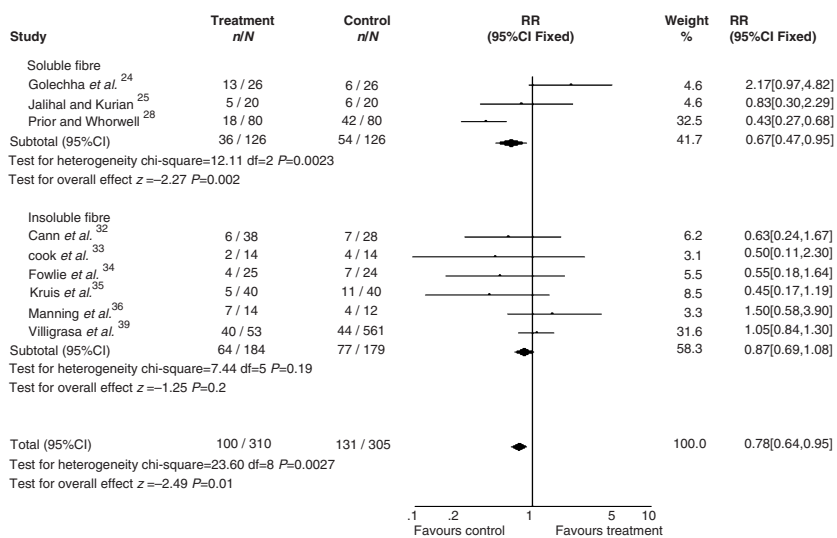


Figure 2. Comparison of different types of fibre and control treatment on irritable bowel syndrome-related abdominal pain.

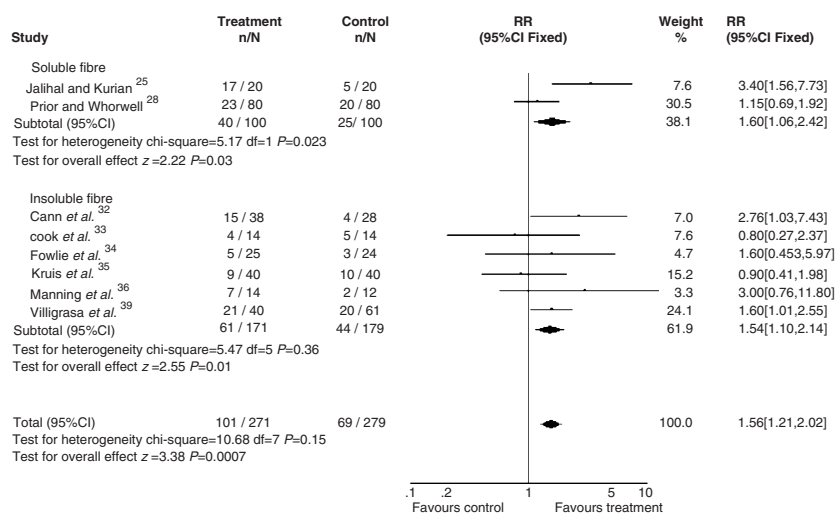
n:number of events in treatment or control group; N: number of participants in treatment or control group; RR: relativrisk

placebo.²³ One study showed that ispaghula was more effective than wheat bran in the treatment of irritable bowel syndrome.³⁰ Global irritable bowel syndrome symptom improvement in patients treated with ispaghula was found in five of seven studies.^{25, 27-30} Pooling the results showed that the relative risk of global symptom relief was 1.55 (95% CI, 1.35-1.78). The proportion of successfully treated patients on active therapy was 64% (Figure 1). The three studies that measured relief from abdominal pain showed conflicting

results (Figure 2).²⁴⁻²⁶ Finally, the overall effect of soluble fibre (ispaghula) was found to be favourable in constipated irritable bowel syndrome patients, although it involved only two studies (Figure 3).^{25, 28}

Efficacy of insoluble fibre

Two of the six studies of wheat bran showed improvement in irritable bowel syndrome symptoms.^{32, 36} Only one study of corn fibre found improvement in pain



n: number of events in treatment or control group; N: number of participants in treatment or control group; RR: relativetisk

Figure 3. Comparison of different types of fibre and control treatment on irritable bowel syndrome-related constipation.

severity, stool frequency and stool consistency, but there was no significant difference compared with placebo.³³ The single study of miller bran found that irritable bowel syndrome symptoms were not improved with miller bran compared with placebo.³⁸ None of the studies showed that bran was better than placebo on the outcome measure of global irritable bowel syndrome symptom improvement (Figure 1). Indeed, global symptoms worsened with both insoluble fibre and placebo, but there was no significance difference between the two (relative risk, 0.89; 95% CI, 0.72–1.11). The six studies that reported on the outcome measure of relief of abdominal pain found considerably different results (Figure 2). Improvement of constipation was found in four of the six studies.^{32, 34, 36, 39} Although the results varied to a great extent in irritable bowel syndrome patients with constipation, overall, insoluble fibre (wheat bran) showed favourable results (relative risk, 1.54; 95% CI, 1.10–2.14) on this outcome measure (Figure 3).

DISCUSSION

This systematic review shows that there is limited and conflicting evidence for the effectiveness of fibre in the treatment of irritable bowel syndrome symptoms. For the measure of efficacy, i.e. the proportion of patients with global irritable bowel syndrome symptom improvement, fibre was significantly better than control. Fibre therapy also showed favourable results in irritable

bowel syndrome-related constipation. However, it may increase abdominal pain in some irritable bowel syndrome patients. The effect of psyllium on constipation was based on only two studies: Jalihal and Kurian²⁵ with a dose of 30 g and Prior and Whorwell²⁸ with a dose of approximately 5 g. Pooling with other studies with a lower dosage might underestimate the effects of a reasonable dose of psyllium.

The two types of fibre, soluble and insoluble, affected irritable bowel syndrome symptoms differently. Soluble fibre was beneficial to global symptom improvement, whereas insoluble fibre was not more effective than placebo and may, in some irritable bowel syndrome patients, worsen symptoms when compared with a normal diet. In two studies, a considerable effect was found. In one of these, a reasonable dose of psyllium was used.²⁵ Toskes *et al.* used calcium polycarbophil, which is a synthetic fibre resistant to bacterial degradation.²⁹ Pooling of these studies with other psyllium studies that use sub-optimal doses underestimates the treatment effect.

Evidence for the effectiveness of soluble fibre was obtained from the pooled results. Irritable bowel syndrome patients treated with this type of fibre reported 1.3 times more global improvement than controls. The effect of soluble fibre on irritable bowel syndrome-related abdominal pain, however, was controversial. Indeed, the studies that reported on the outcome measure of relief of abdominal pain varied considerably and showed conflicting results.^{24, 25, 28}

The efficacy of insoluble fibre in the treatment of irritable bowel syndrome patients was also controversial. The studies showed that diets with a large amount of insoluble fibre might actually be worse than a normal diet. The clinical improvement of irritable bowel syndrome patients treated with insoluble fibre was no better than that obtained with placebo.^{33, 34, 37, 38}

The outcomes used in each of the randomized trials varied considerably. Consequently, several important outcomes were reported in only some of the trials. Moreover, they were measured in different ways. Generic outcomes, such as the quality of life, were not used in any of the trials. In terms of both global irritable bowel syndrome symptom improvement and individual symptom improvement, the studies showed heterogeneous results. The main reason for this may be the small sample sizes studied, which could have produced type II errors. Two studies in our analysis used either a single-blind or an open allocation of intervention,^{36, 39} whereas it is recommended that double-blind assessment should be used in irritable bowel syndrome trials.⁴⁰ However, many difficulties are encountered in the design and execution of trials with dietary intervention. As blinding is difficult in trials evaluating high-fibre dietary advice, we accepted these studies.

Three studies were excluded from our analysis as no data could be extracted to calculate a relative risk. None of these showed a positive response to treatment. This might have given rise to an over-estimation of the effectiveness of fibre.

The majority of patients with irritable bowel syndrome are managed in primary care.⁴ Unfortunately, none of the selected studies included patients treated in a primary care setting. This limits the external validity of our results. Irritable bowel syndrome patients in primary care may, in fact, respond differently to dietary therapy than referred patients.⁴¹ Furthermore, primary care patients who respond to treatment with bulking agents are less likely to be referred to a hospital clinic. Moreover, more than half of the symptomatic 'patients' from the general population do not even present to their general practitioner. The efficacy of fibre in this population is unknown.

The role of fibre in the pathophysiology of irritable bowel syndrome remains poorly understood.⁴² An increase in the amount of dietary fibre is an almost universal recommendation in the primary care management of irritable bowel syndrome,^{3, 5} and guidelines on irritable bowel syndrome management for out-clinic

patients advise an increase in fibre intake in the event of constipation.^{5, 43} However, our review showed only limited support for this recommendation.

In summary, our systematic review demonstrates the effectiveness of fibre therapy in irritable bowel syndrome patients, but only in terms of either global symptom improvement or constipation. The effectiveness on individual symptoms is variable. There is no effect of fibre in irritable bowel syndrome-related abdominal pain. Soluble and insoluble fibre have different effects on global irritable bowel syndrome symptoms. Insoluble fibre is probably no better than placebo and may, in some patients, even worsen the clinical outcome. For the development of evidence-based management guidelines, valid clinical studies in primary care patients, focusing on the effectiveness and tolerability of soluble and insoluble fibre, are needed.

REFERENCES

- 1 Thompson WG, Longstreth GF, Drossman DA, *et al.* Functional bowel disorders and functional abdominal pain. *Gut* 1999; 45(Suppl. II): II43-7.
- 2 Drossman DA, Whitehead WE. Irritable bowel syndrome: a technical review for practice guideline development. *Gastroenterology* 1997; 112: 2120-37.
- 3 Francis CY, Whorwell PJ. The irritable bowel syndrome. *Postgrad Med J* 1997; 73: 1-7.
- 4 Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. *Gut* 2000; 46: 78-82.
- 5 Paterson WG, Thompson WG, Vanner SJ, *et al.* Recommendations for the management of irritable bowel syndrome in general practice. *Can Med Assoc J* 1999; 161: 154-60.
- 6 Bennett WG, Cerda JJ. Benefits of dietary fibre, myth or medicine? *Postgrad Med* 1996; 99: 153-6, 166-72, 175.
- 7 Janssen HAM, Borghouts JAJ, Muris JWM, *et al.* Health status and management of chronic non-specific abdominal complaints in general practice. *Br J Gen Pract* 2000; 50: 375-9.
- 8 Thompson WG, Heaton KW, Smyth CG, *et al.* Irritable bowel syndrome: the view from general practice. *Eur J Gastroenterol Hepatol* 1997; 9: 689-92.
- 9 Friedman G. Diet and irritable bowel syndrome. *Gastroenterol Clin North Am* 1991; 20: 313-24.
- 10 Muller-Lissner S. Effect of wheat bran on weight of stool and gastrointestinal transit time: a meta-analysis. *Br Med J* 1988; 296: 615-7.
- 11 Spiller RC. Pharmacology of dietary fibre. *Pharmacol Ther* 1994; 62: 407-27.
- 12 Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. *Lancet* 1994; 344: 39-40.
- 13 Thompson WG. Doubts about bran. *Lancet* 1994; 344: 3.
- 14 Klein KB. Controlled treatment trials in the irritable bowel syndrome: a critique. *Gastroenterology* 1988; 95: 232-41.

- 15 Rees GA, Trevan M, Davies G. Dietary fibre modification and the symptoms of irritable bowel syndrome — a review. *J Hum Nutr Diet* 1994; 7: 179–89.
- 16 Camilleri M. Review article: clinical evidence to support current therapies of irritable bowel syndrome. *Aliment Pharmacol Ther* 1999; 13: 48–53.
- 17 Jailwala J, Imperiale TF, Kroenke K. Pharmacologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. *Ann Intern Med* 2000; 133: 136–47.
- 18 Akehurst R, Kaltenthaler E. Treatment of irritable bowel syndrome: a review of randomised controlled trials. *Gut* 2001; 48: 272–82.
- 19 Review Manager (RevMan), Version 4.1 for Windows. Oxford: The Cochrane Collaboration, 2000.
- 20 Arfmann S, Andersen JR, Hegnhøj J, *et al.* The effect of coarse wheat bran in the irritable bowel syndrome. A double blind crossover study. *Scand J Gastroenterol* 1985; 20: 295–8.
- 21 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.
- 22 Mortensen PB, Andersen JR, Arfmann S, *et al.* Short-chain fatty acids and the irritable bowel syndrome: the effect of wheat bran. *Scand J Gastroenterol* 1987; 22: 185–92.
- 23 Arthurs Y, Fielding JF. Double blind trial of ispaghula poloxamer in irritable bowel syndrome. *Ir Med J* 1983; 76: 253.
- 24 Golechha AC, Chadda VS, Chadda S, *et al.* Role of ispaghula husk in the management of irritable bowel syndrome (a randomized double blind crossover study). *J Assoc Physicians India* 1982; 30: 353–5.
- 25 Jalihal A, Kurian G. Ispaghula therapy in irritable bowel syndrome: improvement in overall well being related to reduction in bowel dissatisfaction. *J Gastroenterol Hepatol* 1999; 5: 507–13.
- 26 Longstreth GF, Fox DD, Youkeles L, *et al.* Psyllium therapy in the irritable bowel syndrome. A double blind trial. *Ann Intern Med* 1981; 95: 53–6.
- 27 Nigam P, Kapoor KK, Rastog CK, *et al.* Different therapeutic regimens in irritable bowel syndrome. *J Assoc Physicians India* 1984; 12: 1041–4.
- 28 Prior A, Whorwell PJ. Double blind study of ispaghula in irritable bowel syndrome. *Gut* 1987; 28: 1510–3.
- 29 Toskes PP, Connery KL, Ritchey TW. Calcium polycarbophil compared with placebo in the irritable bowel syndrome. *Aliment Pharmacol Ther* 1993; 7: 87–92.
- 30 Ritchie JA, Truelove SC. Treatment of irritable bowel syndrome with lorazepam, hyoscine butylbromide and ispaghula husk. *Br Med J* 1979; 1: 376–8.
- 31 Ritchie JA, Truelove SC. Comparison of various treatments for irritable bowel syndrome. *Br Med J* 1980; 281: 1317–9.
- 32 Cann PA, Read NW, Holdsworth CD. What is the benefit of coarse wheat bran in patients with irritable bowel syndrome? *Gut* 1984; 25: 168–73.
- 33 Cook IJ, Irvine EJ, Campbell CJM, *et al.* Effect of dietary fibre on symptoms and rectosigmoid motility in patients with irritable bowel syndrome. A controlled, crossover study. *Gastroenterology* 1990; 98: 66–72.
- 34 Fowlie S, Eastwood MA, Prescott R. Irritable bowel syndrome: assessment of psychological disturbance and its influence on the response to fibre supplementation. *J Psychosom Res* 1992; 36: 175–80.
- 35 Kruis W, Weinzierl M, Schussler P, *et al.* Comparison of the therapeutic effect of wheat bran, mebeverine and placebo in patients with irritable bowel syndrome. *Digestion* 1986; 34: 196–201.
- 36 Manning AP, Harvey RF, Heaton KW. Wheat fibre and irritable bowel syndrome. A controlled trial. *Lancet* 1977; 1: 419–21.
- 37 Snook J, Shepherd HA. Bran supplementation in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 1994; 8: 511–4.
- 38 Soltoft J, Gudmand-Hoyer E, Krag B, *et al.* A double blind trial of the effect of wheat bran on symptoms of irritable bowel syndrome. *Lancet* 1976; 2: 270–2.
- 39 Villigrasa 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(Suppl. 1): 67–70.
- 40 Veldhuyzen van Zanten SJO, Tally NJ, Bytzer P, *et al.* Design of treatment trials for functional gastrointestinal disorders. *Gut* 1999; 45(Suppl.): 69–77.
- 41 Longstreth GF, Hawkey CJ, Mayer EA, *et al.* Characteristics of patients with irritable bowel syndrome recruited from three sources: implications for clinical trials. *Aliment Pharmacol Ther* 2001; 15: 959–64.
- 42 Whorwell PJ. The problem of gas in irritable bowel syndrome. *Am J Gastroenterol* 2000; 95: 1735–41.
- 43 Jones J, Boorman J, Cann P, *et al.* British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. *Gut* 2000; 47(Suppl. II): ii1–19.