Irritable bowel syndrome in primary care

C.J. Bijkerk

CIP gegevens Koninklijke Bibliotheek Den Haag.

Bijkerk, CJ
Irritable Bowel Syndrome in primary care
Thesis, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands, with a summary in Dutch.

ISBN: 978-90-393-4744-7
Cover: Ruud van der Lubben fotografie
Print: Gildeprint Drukerijen BV, Enschede

Irritable bowel syndrome in primary care

Prikkelbare darm syndroom in de huisartsenpraktijk

(met een samenvatting in het Nederlands)

Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit van Utrecht op gezag van de rector magnificus, prof. dr. J.C. Stoof, in gevolge van het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 26 februari 2008 des middags te 16.15 uur

door

Cornelis Johannes Bijkerk

Geboren op 6 augustus 1972
te Steenwijkerwold

Promotores
prof. dr. A.W. Hoes[1]
prof. dr. J.A. Knottnerus[2]

Co-promotores
dr. N.J. de Wit[1]
dr. J.W.M. Muris[2]

1 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands.
2 Care and Public Health Research Institute (CAPHRI), Department of General Practice, Maastricht University, the Netherlands.

The studies presented in this thesis were supported by grants from the Dutch Health Care Insurance Board (CVZ), the Netherlands Organisation for Scientific Research (ZonMw) and Pfizer B.V., the Netherlands.

The author gratefully acknowledges financial support for printing this thesis by the Julius Center for Health Sciences and Primary Care and Janssen-Cilag B.V., the Netherlands.

Contents

Thesis Committee
prof. dr. A.P.M. Smout
prof. dr. Y. van der Graaf
prof. dr. H.E. van der Horst
prof. dr. P.J. Whorwell

Chapter 1

General introduction

Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain or discomfort is associated with a change in bowel habit, or with features of disordered defecation.(1) Because there are no biological markers to define this disorder, investigators attempted to define IBS using symptom-based criteria, derived from epidemiological investigations. The Manning criteria, for example, drawn up in 1978, list abdominal pain, altered bowel habits, mucus in stools, and bloating as the major signs of IBS. These criteria have been widely used ever since their development even though validation has proven very difficult.(2) As a result, gastroenterologists developed diagnostic criteria for IBS and other functional gastrointestinal disorders by consensus. These so called Rome-criteria were first developed in 1990 (Rome I) and updated in 1999 (II) and 2006 (III). The Rome criteria have been widely used for clinical research.(3) The key factor in the Rome criteria for IBS is abdominal pain lasting longer than 3 months. Figure 1 shows the Rome III diagnostic criteria for IBS.(4) The Rome criteria for IBS are primarily designed for use in hospital-based research and their validity for use in primary care is not well established. Most general practitioners (GPs) use more pragmatic practice-based criteria.(5-8) In the Dutch College of General Practitioners (NHG) guideline IBS is defined as a chronic gastrointestinal disorder characterized by recurrence of abdominal pain or bloating in relation to disturbed bowel habits. Mucus without blood in the stools, the presence of a palpable, tender colon and discomfort during rectal examination has been proposed to support the diagnosis of IBS.(9) IBS patients are often categorised according to their predominant bowel habit as IBS with constipation (IBS-C), IBS with diarrhoea (IBS-D), or IBS with alternating constipation or diarrhoea (IBS-A).

Figure 1. Rome III Diagnostic criteria for irritable bowel syndrome*

Recurrent abdominal pain or discomfort** at least 3 days per month in the last 3 months associated with *2 or more* of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

* Criteria fulfilled for the last 3 months with symptoms onset at least 6 months prior to the diagnosis.

** Discomfort defined as an uncomfortable sensation not described as pain. In pathophysiological research and clinical trials, a pain/discomfort frequency of at least 2 days per week during screening is required for eligibility.

Epidemiology

IBS is the most common gastrointestinal (GI) disorder. In epidemiological studies the reported prevalence of IBS varies, but this is mainly attributed to differences in diagnostic criteria. In the (adult) population the prevalence is estimated at 9%.(10) The prevalence of IBS is higher in women and there is a decrease in the reported frequency among older individuals.(11) In the majority of patients the initial symptoms develop between the age of 30 and 50 years. In up to 30% the first symptoms occur after a gastrointestinal infection.(12;13) It is estimated that only 20-25% of patients with IBS seek medical advice.(14) The reported incidence of IBS in primary care is 4-13/1000 patients per year. A general practitioner sees on average 1-2 IBS patients per week. Most patients are managed in primary care and less than 5% of these patients is referred to hospital specialists.(15) Major reasons for referral include alarm symptoms, uncertainty about the diagnosis, excessive patient concerns and persistent symptoms with severe impairment of the patient's functioning. IBS patients generally have high consultation rates, both for IBS as well as other symptoms. Most patients have a long standing disease history and chronic patients experience serious impact on quality of life. The prevalence of typical disease characteristics is affected by consultation and referral.(16) Consulting IBS patients do have a different psychological profile compared to those who do not consult.(17) Referred IBS patients experience more pain, and more frequently report other IBS complaints compared to those in primary care.(15)

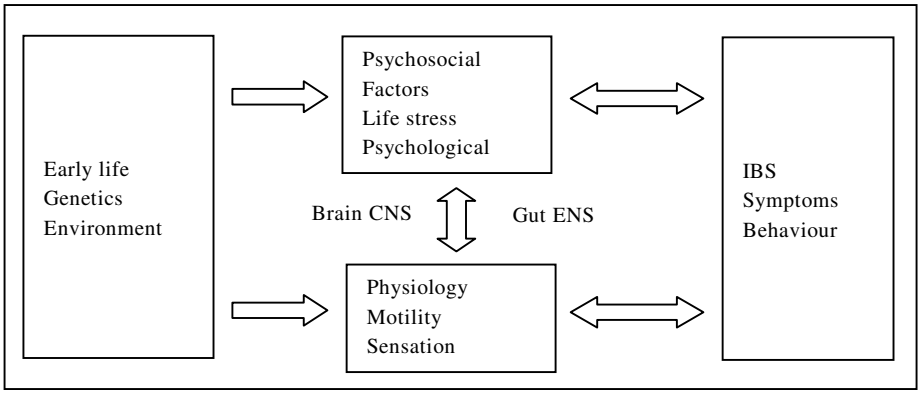
Patients with IBS have an increased prevalence of somatic and psychiatric comorbidity and a higher burden of major life events. Comorbidity increases as the severity of IBS increases and may be associated with psychological factors.(18)

Pathophysiology

Although many pathophysiological explanations have been suggested for IBS, no unique mechanism has been identified. Rather, it seems that the same mechanisms are responsible for abdominal pain and altered bowel habits in people with and without IBS. IBS can best be explained using a bio-psychosocial model.(19-22) Figure 2 shows a conceptual model for the pathogenesis of IBS and the relationships between psychosocial and physiological factors and IBS symptoms. Available studies indicate that IBS symptom generation is related to disturbances in brain-gut interactions. The brain-gut axis may be modulated by abnormal central processing, autonomic and hormonal events, genetic and environmental factors, psychological disturbance and postinfectious sequellae. Genetic factors, in addition to environmental factors such as family influences on illness expression, major life

events or exposure to GI infection, may affect one's suspectability to gut dysfunctioning, either through abnormal motility, visceral hypersensitivity or mucosal inflammation. In the central nervous system, the locus of intestinal symptom control is situated mainly in the limbic system, which also plays a central role in emotional response and is involved in the 'top-down' modulation of visceral perception.(23)

Figure 2. Biopsychosocial conceptualization of the pathogenesis of IBS



CNS, central nervous system; ENS, enteric nervous system.

Senso-motoric dysfunctioning

Disturbance of the interaction between the brain and the gut and its enteric nervous system (the brain-gut axis) is contributing to altered intestinal motility and increased visceral sensitivity. IBS patients with a moulded central processing of pain respond differently to distension of the colon than healthy controls.(24) These patients may have an abnormal response through an increased visceral pain perception. The endogenous modulation of visceral pain is abnormal in IBS and involves aberrant pain processing. Furthermore, altered control of abdominal visceral muscle activity in these patients may contribute to IBS symptomatology. A number of abnormal sensory and motor patterns (e.g. 5-Hydroxytryptamine serotonin neurotransmitter deficiency) have been reported in patients with IBS. However, it is not known to what extent these pathophysiological changes actually induce symptoms.

The literature to date suggests that IBS patients have an increased sensitivity to painful distension in the colon. This hypersensitivity may be located in mucosal receptors within the gut wall. These receptors may be sensitised by short-chain fatty acids, malabsorbed bile salts, bran, or immunological mechanisms. Some authors suggest that IBS is largely a motility disorder of the colon, involving increased contractility and postprandial mass movements. In addition, motility disturbances of

the small intestine occur in some IBS patients, and even delayed gastric emptying has been observed in IBS patients. However the exact pathophysiological path is unknown and no consistent abnormality of small or large intestinal motility has been identified in IBS.(24)

Many IBS patients attribute their symptoms to specific food substances. Though they are more likely to experience a subjective generalised effect of food ingestion on intestinal activity, so far there is no evidence for food allergy or other dietary causes of IBS. Nevertheless certain dietary substances may aggravate symptoms in some individuals. These may include fatty foods, beans and other gas producing foods, alcohol, caffeine, lactose in lactase deficient individuals, and in some cases excess fibre intake.(25)

Psychopathology

IBS patients have an increased prevalence of psychiatric diagnoses, including personality disorders, anxiety, depression and somatisation.(26) Stress is known to cause exacerbations of bowel symptoms in IBS patients as well as in healthy subjects. Stressful life events have been reported to be more frequent in patients with IBS, but others have questioned this relation.(27;28) A recent study in tertiary care IBS patients confirmed that a psychosocial trauma, such as sexual abuse, leads to a poorer adjustment to illness-associated behaviour, increased reporting of pain and poorer clinical outcome.(29) In addition IBS patients show significant impairments in functional status, more disability and work absenteeism, and more often consult doctors.(30) Although the increased prevalence of comorbidity in IBS patients has been firmly established in cross sectional research, the longitudinal relation between IBS and somatic, functional and psychosocial comorbidity remains unclear. (28;31;32) Detailed historical assessment of comorbidity in IBS might reveal subcategories of IBS patients with different prognosis and characteristics, which might facilitate a more personalised and accurate management in an early stage.

Management

In general the management of IBS is directed by the nature and severity of symptoms, and the extent of psychological disturbance and functional impairment. It is recommended to start with reassurance and counselling and discuss the patient's ideas, fears and expectations.(33) So far the expectations of IBS patients regarding management are not well established.

The majority of GPs provides dietary advice, mainly focussing on increasing the fibre content of the daily diet by adding insoluble fibre (bran). In addition the

majority of the IBS patients receives pharmacotherapy, frequently including bulking agents, in particular psyllium supplements.(34)

Dietary fibre

Dietary fibres are non-fermentable parts of leguminous plants, such as cellulose, bran, psyllium, pectine and ligine. Fibre therapy is cheap and seems, in general, well tolerated. It may give pain relief and improve stool frequency in IBS patients by modulating visceral hypersensitivity and colonic motility. Dietary fibre is usually classified as soluble or insoluble fibre:
Soluble fibre (e.g. psyllium) dissolves in water, 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 gut transit time. This shortened transit time may alleviate constipation and decrease intra-colonic pressure, possibly resulting in a reduction of pain.
Insoluble fibre undergoes minimal changes in the digestive tract. It increases the faecal mass, thus shortening the colonic transit. Some have suggested that insoluble fibre (e.g. bran), may enhance motility of the gut, thus worsening IBS symptoms (35;36)

This thesis

Most IBS patients are managed in primary care, but most therapeutic trials included referred IBS patients only. IBS patients in primary care differ in many aspects from secondary/tertiary care patients and these patient chraracteristics are likely to influence the effect of therapeutic interventions.(15) Therefore methodologically sound clinical trials in primary care are needed to establish evidence-based guidelines. Presently many of the recommendations for management of IBS are based on clinical experience rather than randomised controlled trials (RCT).(37) To establish the efficacy of fibre in the treatment of IBS, we designed and performed a randomised controlled trial studying the effectiveness of soluble (psyllium) and insoluble (bran) fibre in primary care IBS patients. In this trial several methodological challenges were met regarding outcome measurement and patient selection.

In this thesis the results of this trial, are reported and methodological issues relevant to design of such a trial are discussed. In addition, several other relevant aspects of IBS in primary care are studied. The following research questions are addressed:

1. What are the IBS patients' and doctors' perceptions regarding management of IBS?
2. What are the determinants of consultation behaviour in IBS in primary care?
3. What is the historical relation between IBS and somatic and psychosocial comorbidity?
4. What is the preferred outcome measurement in IBS research?
5. Did IBS patients who participated in this RCT differ from those in primary care practice?
6. What is the currently available evidence for the effectiveness of fibre therapy in IBS patients?
7. What is the effectiveness of soluble and insoluble fibre in relieving symptoms in primary care patients with IBS?

Outline of this thesis

In chapter 2 we report the experiences and perceptions of GPs and IBS patients regarding IBS symptoms and management.

Only a minority of the patients with IBS consult their GP. In chapter 3 we report the factors that determine helpseeking behaviour of patients with IBS in primary care.

Somatic and psychosocial comorbidity is very common in IBS patients, but the longitudinal relation is unclear. We analysed 10-year follow-up data of IBS patients in a primary care database. In chapter 4 we report the prevalence of different categories of comorbidity before, during and after the diagnosis of IBS.

In chapter 5 we review the available outcome measures for IBS research and compare their psychometric and methodological properties.

Selective recruitment of patients is a common problem in IBS research, possibly limiting the external validity of the trial results. In chapter 6 we describe the recruitment process of our trial and compared the demographic and disease-specific characteristics of the randomised patients, with those patients that were eligible but non randomised and those that were non-eligible.

To establish the current evidence for the effectiveness of fibre treatment in IBS we performed a systematic review based of available randomised controlled trials. The results are presented in Chapter 7.

In chapter 8 we present the results of the randomised controlled trial assessing the effectiveness of soluble (psyllium) or insoluble (bran) fibre in the management of patients with IBS in primary care.

Finally in chapter 9 we discuss the results of our studies in a primary care perspective, and provide recommendations for daily clinical practice.

References

1. Cayley WE, Jr. Irritable bowel syndrome. BMJ 2005 Mar 19;330(7492):632.
2. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. Br Med J 1978 Sep 2;2(6138):653-4.
3. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. Gut 1999 Sep;45 Suppl 2:II43-II47.
4. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006 Apr;130(5):1480-91.
5. Mearin F, Badia X, Balboa A, Baro E, Caldwell E, Cucala M, et al. Irritable bowel syndrome prevalence varies enormously depending on the employed diagnostic criteria: comparison of Rome II versus previous criteria in a general population. Scand J Gastroenterol 2001 Nov;36(11):1155-61.
6. Vandvik PO, Aabakken L, Farup PG. Diagnosing irritable bowel syndrome: poor agreement between general practitioners and the Rome II criteria. Scand J Gastroenterol 2004 May;39(5):448-53.
7. Janssen HA, Borghouts JA, Muris JW, Metsemakers JF, Koes BW, Knottnerus JA. Health status and management of chronic non-specific abdominal complaints in general practice. Br J Gen Pract 2000 May;50(454):375-9.
8. Oberndorff-Klein Woolthuis AH, Brummer RJ, de Wit NJ, Muris JW, Stockbrugger RW. Irritable bowel syndrome in general practice: an overview. Scand J Gastroenterol Suppl 2004;(241):17-22.
9. Boukes FS, van der Horst HE, Assendelft WJ. (Summary of The Dutch College of General Practitioners' 'Irritable bowel syndrome' standard). Ned Tijdschr Geneeskd 2002 Apr 27;146(17):799-802.
10. Schlemper RJ, van der Werf SD, Vandenbroucke JP, Biemond I, Lamers CB. Peptic ulcer, non-ulcer dyspepsia and irritable bowel syndrome in The Netherlands and Japan. Scand J Gastroenterol Suppl 1993;200:33-41.
11. Jones R, Lydeard S. Irritable bowel syndrome in the general population. BMJ 1992 Jan 11;304(6819):87-90.
12. Hillila MT, Farkkila MA. Prevalence of irritable bowel syndrome according to different diagnostic criteria in a non-selected adult population. Aliment Pharmacol Ther 2004 Aug 1;20(3):339-45.
13. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003 Mar 1;17(5):643-50.

14. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. Gut 2000 Jan;46(1):78-82.
15. Van der Horst HE, van Dulmen AM, Schellevis FG, van Eijk JT, Fennis JF, Bleijenberg G. Do patients with irritable bowel syndrome in primary care really differ from outpatients with irritable bowel syndrome? Gut 1997 Nov;41(5):669-74.
16. Talley NJ, Boyce PM, Jones M. Predictors of health care seeking for irritable bowel syndrome: a population based study. Gut 1997 Sep;41(3):394-8.
17. Koloski NA, Talley NJ, Boyce PM. Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. Am J Gastroenterol 2001 May;96(5):1340-9.
18. Vandvik PO, Wilhelmsen I, Ihlebaek C, Farup PG. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. Aliment Pharmacol Ther 2004 Nov 15;20(10):1195-203.
19. Ohman L, Simren M. New insights into the pathogenesis and pathophysiology of irritable bowel syndrome. Dig Liver Dis 2007 Mar;39(3):201-15.
20. Aziz Q, Thompson DG. Brain-gut axis in health and disease. Gastroenterology 1998 Mar;114(3):559-78.
21. Wilhelmsen I. Brain-gut axis as an example of the bio-psycho-social model. Gut 2000 Dec;47 Suppl 4:iv5-iv7.
22. Kamm MA. The role of psychosocial factors in functional gut disease. Eur J Surg Suppl 1998;(583):37-40.
23. Jones MP, Dilley JB, Drossman D, Crowell MD. Brain-gut connections in functional GI disorders: anatomic and physiologic relationships. Neurogastroenterol Motil 2006 Feb;18(2):91-103.
24. Clemens CH, Samsom M, Roelofs JM, van Berge Henegouwen GP, Smout AJ. Association between pain episodes and high amplitude propagated pressure waves in patients with irritable bowel syndrome. Am J Gastroenterol 2003 Aug;98(8):1838-43.
25. Friedman G. Diet and the irritable bowel syndrome. Gastroenterol Clin North Am 1991 Jun;20(2):313-24.
26. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology 2002 Apr;122(4):1140-56.
27. Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC, et al. Psychosocial factors in the irritable bowel syndrome. A multivariate

study of patients and nonpatients with irritable bowel syndrome. Gastroenterology 1988 Sep;95(3):701-8.
28. Lydiard RB. Irritable bowel syndrome, anxiety, and depression: what are the links? J Clin Psychiatry 2001;62 Suppl 8:38-45.
29. Drossman DA, Leserman J, Nachman G, Li ZM, Gluck H, Toomey TC, et al. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. Ann Intern Med 1990 Dec 1;113(11):828-33.
30. van den Heuvel-Janssen HA, Borghouts JA, Muris JW, Koes BW, Bouter LM, Knottnerus JA. Chronic non-specific abdominal complaints in general practice: a prospective study on management, patient health status and course of complaints. BMC Fam Pract 2006;7:12.
31. Lydiard RB. Anxiety and the irritable bowel syndrome: psychiatric, medical, or both? J Clin Psychiatry 1997;58 Suppl 3:51-8.
32. Vandvik PO, Lydersen S, Farup PG. Prevalence, comorbidity and impact of irritable bowel syndrome in Norway. Scand J Gastroenterol 2006 Jun;41(6):650-6.
33. Van der Horst HE, Schellevis FG, van Eijk JT, Bleijenberg G. Managing patients with irritable bowel syndrome in general practice. How to promote and reinforce self-care activities. Patient Educ Couns 1998 Oct;35(2):149-56.
34. Cardol M, van Dijk L, de Jong JD, de Bakker DH, Westert GP. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Huisartsenzorg: wat doet de poortwachter? Utrecht/Bilthoven: NIVEL/RIVM; 2004.
35. Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. Lancet 1994 Jul 2;344(8914):39-40.
36. Miller V, Lea R, Agrawal A, Whorwell PJ. Bran and irritable bowel syndrome: the primary-care perspective. Dig Liver Dis 2006 Oct;38(10):737-40.
37. Quartero AO, Meineche-Schmidt V, Muris J, Rubin G, de WN. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev 2005;(2):CD003460.

Chapter 2

Irritable bowel syndrome in primary care; the patient's and doctor's views on symptoms, aetiology and management

Published as: Bijkerk CJ, de Wit NJ, Stalman WAB, Knottnerus JA, Hoes AW, Muris JWM. Irritable bowel syndrome in primary care, the patient's and doctor's views on symptoms, aetiology and management. *Can. J Gastroenterol.* 2003;17:363-368.

Abstract

Background: In order to facilitate the development of clinical guidelines and to focus on irritable bowel syndrome (IBS) research, insight into the perceptions of patients and general practitioners (GPs) regarding IBS is required.
Aim: To compare patients' and GPs' views on the symptomatology, aetiology, and treatment of IBS.
Methods: 142 IBS patients and 100 GPs were requested to complete a structured questionnaire.
Results: The response rates of the patients and GPs were 80% and 47%, respectively. Although all patients were diagnosed by their GP as having IBS, only 18% fulfilled the Rome II criteria for IBS and 62% the Manning criteria. The Manning criteria coincided well with the GPs' standards. In both the patients' and doctors' views, IBS is related to food and stress. Initial management of IBS by the GPs starts with dietary advice (94%), counselling (77%), and drug therapy (55%). A majority of the patients reported therapeutic gain from pharmacotherapy, and noted that dietary interventions were less appreciated.
Conclusions: Patients and GPs agree on IBS symptomatology, as outlined in the Manning criteria. Although GPs and patients consider stress and diet important aetiological factors, pharmacotherapy remains the cornerstone of IBS management in primary care patients.

Introduction

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterised by recurrent episodes of abdominal pain, altered bowel habits, and/or symptoms of bloating and abdominal distension. This symptom complex is currently the most common gastrointestinal disorder seen in primary care.(1,2) It has been suggested that patients and doctors have different experiences and expectations with regard to IBS and its treatment. If this is true, it is of major importance that both patients' and doctors' views on the symptomatology, aetiology, and management of IBS be explored, for maximal compliance with future IBS guidelines and for an optimal focus of future research.

Various diagnostic criteria for IBS have been developed at the secondary care level in order to discriminate between IBS and organic disorders. Although both the Manning (3) and the Rome criteria (4)(5)may be applicable in the primary care setting, many general practitioners (GPs) use their own standards.(6) Most GPs are also quite confident about their diagnosis of IBS.(7)

Although it is often suggested that IBS symptoms are triggered by stress or dietary indiscretions,(8) the actual pathophysiological course of this syndrome is as yet unknown. In fact, research to date indicates that symptoms of IBS may be generated by a wide spectrum of factors, including abnormal mobility, increased sensitivity of the gut, inflammation, psychological factors, dietary factors, and disturbed brain-gut interactions. IBS symptoms are often attributed to specific food substances; however, little is known about the views of primary care IBS patients regarding the relation diet-symptomatology. Many patients also relate symptom severity to stress and anxiety.(9,12) The impact of IBS on patient's lifestyle can be more precisely described using a health-related quality of life (HRQOL) measurement. This measure evaluates symptom perception, illness experience, and functional health status in relation to an illness.(8) So far, however, studies evaluating the HRQOL in primary care IBS patients are scarce.

In the management of IBS counselling and reassurance constitute the first-choice management of most GPs.(7,13) Others, have noted that most GPs also give dietary advice and frequently prescribe medication.(14,15) Guidelines for the management of IBS are scarce and evidence for therapeutic interventions in IBS is lacking.(1,16,17) Regardless of the type of management, a good patient-doctor relationship is of prime importance in the management of functional bowel disorders like IBS.(18) This is supported by the observation that many IBS patients feel insufficiently informed, particularly with regard to the background of the disease and treatment options, that some even feel stigmatised and let down by their

doctor.(6,19,20) Such disappointment suggests that patients and doctors have different ideas about IBS management.
To date, patients' expectations regarding the management of IBS have not been explored in depth and, even though many treatment modalities are used, little is known about the goals that GPs set for treatment. In this survey, therefore we aimed to evaluate both the patients' and GPs' standpoints on IBS, with special emphasis on the perceptions of symptoms, personal views on contributory factors, and expectations from management.

Methods

We performed an observational study amongst 142 primary care IBS patients and 100 GPs from the Utrecht and Maastricht (The Netherlands) areas. Patients were randomly selected from the Utrecht General Practitioners Network (HNU), a network of 20 GPs working in six health centres affiliated with the University Medical Center of Utrecht. The HNU database contains information about the health problems and GP consultations of more than 50,000 primary care patients. Health problems have been systematically coded in the database, for almost 10 years, using the International Classification of Primary Care (ICPC).(21) Searching this database, we identified all patients aged 18-65 years, who were assigned the ICPC code D93 (irritable bowel syndrome) at least twice during the previous 4 years. Patients in this sample (n=732) were then divided in three groups: "prevalent" IBS patients (patients who had consulted for IBS at least twice in both of the previous two years); "incident" IBS patients (new patients with a diagnosis of IBS in the previous year) and "latent" IBS patients (patients who did not consult for IBS complaints in the previous year, but had done so more than twice in the years before). All "prevalent" IBS patients (n=42), and a weighted random sample of 50 "incident" and 50 "latent" cases, (total 142 IBS patients) were sent a postal questionnaire.

Questionnaire

The questionnaire was based on the Bowel Disease Questionnaire (BDQ), developed by Tally et al.(22) The BDQ is a validated instrument for identifying IBS patients in the population at large. In addition to questions on demographic variables, abdominal and bowel symptoms, related complaints, and possible causes, we incorporated both the Manning (3) and Rome II (5) criteria for IBS in order to test the efficacy of these diagnostic criteria in primary care (Figure 1). We also included questions about impairments of daily activities and work absenteeism, and asked patients about their views on relevant outcome parameters of IBS. Health-related quality of life was assessed using the Irritable Bowel Syndrome Quality of Life

Questionnaire (IBSQOL).(23) The IBSQOL was proven valid in an earlier study and a Dutch translation became available recently.(24) To facilitate comparisons, we transformed the scores so that they ranged from 0 to 100 (100 being the highest possible score, representing maximal quality of life). A letter of invitation signed by the patient's GP accompanied the questionnaire. Non-responders received a written reminder. If necessary, they were contacted by the general practitioners' practice assistant. One hundred GPs randomly selected from the Utrecht and the Maastricht University Primary Care Networks, 50 from each centre, received a postal questionnaire regarding their views on diagnostic criteria, management, and treatment goals in IBS. Non-responding GPs received a reminder.

Statistic analysis

The questionnaires were coded for analysis. Data analysis was performed with SPSS software using descriptive statistics and cross-tabulations. Student t-tests were used for subgroup analyses in the three different patient groups ("prevalent", "incident", "latent" IBS patients) and the two GP groups ("Utrecht" and "Maastricht").

Figure 1. Manning and Rome II diagnostic criteria for irritable bowel syndrome

Rome II criteria: Abdominal discomfort or pain for at least 12 or more consecutive weeks in the preceding 12 months, with at least two of the tree following features:

1. Relief with defecation; and/or
2. Onset associated with a change in looser stool frequency; and/or
3. Onset associated with a change in stool consistency.

Manning criteria: Abdominal pain with 2/3 or more of the following features:

1. Abdominal pain relieved by defecation; and/or
2. Abdominal pain associated with more frequent stools; and/or
3. Abdominal pain associated with looser stools; and/or
4. Abdominal distension or bloating; and/or
5. Feeling of incomplete defecation; and/or
6. Mucus in stools

Results

Of the 142 patients randomly selected patients from the Utrecht General Practitioners Network (HNU), 25 (18%) did not meet the inclusion criteria retrospectively. Reasons for this were uncertainty of the IBS diagnosis (11 patients), an organic disorder during follow-up (10 patients), and severe psychiatric comorbidity (4 patients). In addition, 18 patients (13%) had to be excluded due to admission to hospital or nursing home (7 patients) or inability to fill out the questionnaire due to poor condition or language problems (11 patients). Of the 99 remaining patients, 79 returned their questionnaires (response rate 80%). The mean

age of the respondents was 44.5 years (SD = 17.4 years). There were no significant differences in age or gender between the "prevalent", "incident", and "latent" IBS patients. The response rate of the GP questionnaire was 47% (47/100). There were no significant differences in response rate, age, or gender between the GP groups from the two university networks.

Diagnostic criteria for IBS

Although all patients were diagnosed with IBS by their GP as having IBS, only a minority (18%) reported symptoms that completely fulfilled the Rome II diagnostic criteria for IBS (Table 2). In contrast, 67% of the patients reported two key symptoms consistent with the Manning criteria for IBS, and almost half reported having three or more Manning criteria (Table 1).

The diagnostic criteria for IBS that were frequently reported by general practitioners included bloating or a feeling of abdominal distension (87%) and the absence of alarming features (87%). Although only two GPs (4%) reported being familiar with either the Manning or Rome criteria for IBS, 63% stated that they considered continuous or recurrent abdominal pain lasting more than three months during the previous year - which is the core symptom in the Rome II definition of IBS - to be the crucial symptom in defining IBS. Other criteria used in the Rome II definition (e.g., relief after defecation, altered frequency of stool, and changed consistency of stool) were less frequently reported (by 33%, 22%, and 35% of the GPs, respectively).

Table 1. Classification of IBS according to Rome and Manning criteria as reported by the patients

Definition of IBS	N	%
Rome II ≥2	14	18
Manning ≥2	48	62
Manning ≥3	37	47

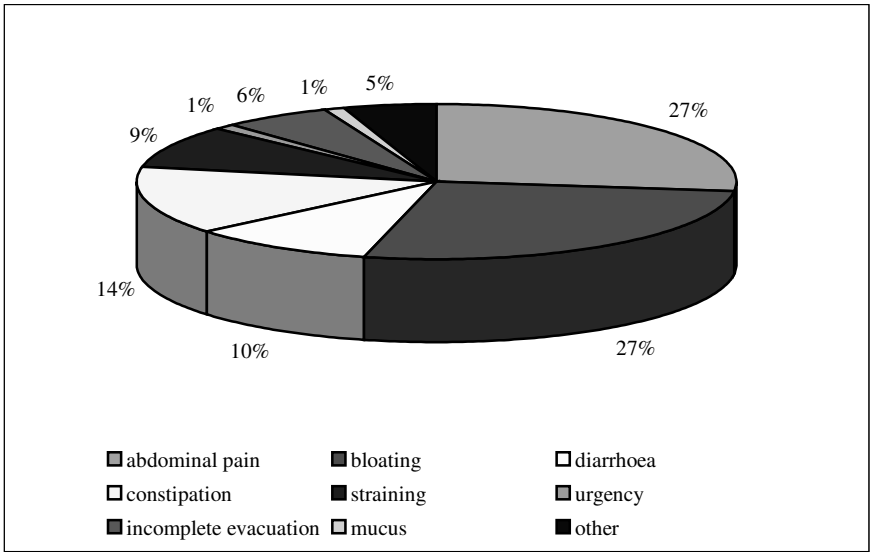
Forty-nine percent of the GPs reported that their primary focus in diagnosing IBS was to exclude an organic disorder. The majority (67%), however, considered diagnostic investigations only necessary in exceptional cases: 9% reported finding a once-in-a-life time endoscopy useful. The diagnostic strategy obviously depended on the patient's age: laboratory tests (48%) and endoscopies (36%) were often reported as part of standard diagnostic IBS management IBS in primary care patients over 50 years of age. Patients under 50 years were rarely referred for diagnostic investigations.

Symptomatology in IBS

More than half of the responding patients reported having symptoms on a weekly or even daily basis during the previous year (Table 2). Seventy percent reported having intermittent symptoms. In retrospect, patients reported a median abdominal pain score of 2.00 (SD =1.85) on a scale of 1-4 in the active phase of their IBS. Symptom severity was reported as moderate to severe by the majority (63%) of the respondents, mild by 19%, and very severe by 10%. Almost half of the patients reported a history of abdominal complaints lasting more than 10 years, while only 6% noted that the symptoms had occurred within the last year. Bloating-predominant IBS was the most frequently reported subtype of IBS (Table 2). There were no statistically significant differences between the "prevalent", "incident", and "latent" patients with regard to the above items. Patients reported bloating (27%) and abdominal pain (27%) as the most bothersome symptoms (Figure 2), while complaints such as diarrhoea (10%), constipation (14%), and related symptoms (straining (9%), urgency (1%), and feelings of incomplete evacuation (6%)) were considered minor problems. Only one patient reported mucus as the most bothersome symptom. These observations were in line with the doctors' views on symptomatology: almost all GPs considered abdominal pain and bloating as the most characteristic IBS symptoms (95% and 86%, respectively).

Heartburn was reported by 32% of the IBS patients and dyspeptic symptoms by 79%. Belching, borborygmus, and flatulence were also frequently reported (42%, 64%, and 67%, respectively). Furthermore, concomitant pain syndromes were prevalent: 61% reported headache, 65% lower backache, and 66% arthralgia or muscle pains. Fatigue and anorexia were reported by 47% and 26% of the patients, respectively. Urinary tract symptoms were rare (16%). Half of the patients reported psychological problems like sleeplessness (36%), nervousness (51%), and depressed feelings (59%): 25% reported a major depression during the previous year and 22% an anxiety disorder. Again, there were no significant differences between the different patient groups with regard to these items.

Figure 2. Patients' views of IBS symptomatology (n=79), distribution of most bothersome symptoms (%)



Aetiology of IBS

Patients frequently considered either a somatic cause (39%), food intolerance (37%), or stress (43%) the cause of their IBS symptomatology; they often noted a family factor as well (11%). Also, there were no significant differences between the three IBS patients groups with regard to this line of thinking. Twenty-one percent of the patients reported having food intolerance for one or more food products, with intolerance for soda, fat, and spicy foods being the most frequently reported (42%, 58%, and 60%, respectively). Provocation of IBS symptoms by dairy products (e.g. cheese and milk) was less frequently reported (9% and 16%, respectively). Seventy-five percent reported having excluded one or more "less" tolerated food products from their diet. The majority (81%) of them noted symptom improvement afterwards. Sixteen percent of the patients could not tolerate dietary fibre, while one fifth reported benefiting from a high-fibre diet.

Most GPs considered stress, fibre deficiency, and disturbed motility to be the most important causative factors (71%, 83%, and 62%, respectively). The GPs reported other etiologic factors such as hypersensitivity (26%), food intolerance (4%), or brain-gut disturbance (4%) less frequently.

Table 2. Symptomatology as reported by IBS patients (n=79)

	N	%
Frequency of IBS symptoms		
Daily or more than once a week	31	44
Once a week	13	18
A few times a year	15	21
Course of complaints during previous 4 weeks		
Improvement	22	29
No change	39	52
Worsening	13	17
History of abdominal complaints		
< 1 year	4	6
1-2 years	9	11
2-5 years	17	22
5-10 years	9	12
> 10 years	38	49
Predominant IBS symptom		
Pain	13	16
Bloating	33	42
Constipation	15	19
Diarrhoea	7	9
Alternating defecation	8	10

IBS was found to have a moderate impact on the quality of life (QOL), as measured by the IBSQOL. It severely affected sexual functioning and caused a mild to moderate impairment of physical and emotional QOL dimensions (Table 3). Patients reported a productivity score over the past four weeks of 77 (mean, SD 26) on a 100-mm Visual Analogue Scale. More than one third of the respondents reported an IBS-related absenteeism from work, on average 15 days over the past year (Table 3).

Management

With regard to IBS management, patients expected reassurance and counselling from their doctor (mentioned by 47 and 30%, respectively, Table 4). Pharmacotherapy, diagnostic tests, and referral were also commonly desired, while dietary interventions are less warranted. Most patients indicated that improvement of abdominal pain, bloating, or stool frequency should be the primary goal of treatment (35%, 46%, and 37%, respectively), while 8% and 11%, respectively mentioned global improvement of symptoms and improvement in QOL as the optimal outcome of treatment.

Table 3. Quality of life and productivity in primary care IBS patients. QOL scored on the IBSQOL using nine subscales (0= minimum, 100=optimal)

	N	mean	SD
IBS QOL subscales			
Emotional	66	65.6	20.6
Mental health	67	75.3	34.8
Sleep	75	79.4	19.3
Energy	74	74.3	19.0
Physical functioning	69	58.1	35.9
Food	75	71.7	39.0
Social role	73	79.6	38.0
Physical role	72	63.4	21.0
Sexual relations	71	29.3	21.3
Productivity			
Productivity during previous 4 weeks	66	77	27
Absenteeism days (median, range)	32	15	(1-104)
Less-productive days (median, range)	24	21	(1-181)

When asked for their experiences with IBS treatment, one third of the patients reported adequate relief of IBS symptoms after reassurance and counselling by their GP (34%). A minority of the patients (13%) had been treated with antispasmodic drugs. Half (53%) of them reported subsequent symptom improvement. One third of the patients benefited from treatment with fibre supplements (32%). Of the 61% who had been referred to a dietician, only 8% reported benefiting from dietary advice.

Most general practitioners noted that dietary advice (94%) and counselling (79%) were of paramount importance in the treatment of IBS. Sixty-three percent provided standard lifestyle advice and 4% behavioural therapy. More than half of the GPs (55%) started IBS management with pharmacotherapy, most frequently with fibre supplements (67%) and antispasmodics (25%) (Table 5). When asked about their treatment goals, most GPs (70%) preferred to stop pharmacotherapy for IBS as soon as the patient reported global symptom improvement. For a minority, cessation of treatment was decided purely on the improvement of the predominant symptom (28% on improvement abdominal pain, 24% on bloating). Ten percent of the GPs reported prescribing life-time therapy with fibre supplements or antispasmodics.

Table 4. Patients' expectations of the type of IBS management when consulting their doctor (n=79)

	N	%
Counselling	33	47
Reassurance	21	30
Dietary advice	7	10
Pharmacotherapy	26	37
Diagnostic tests	27	38
Referral dietician	7	9
Referral specialist	28	39

Table 5. Standard GPs' management in IBS patients (n=47)

	N	%
Counselling	35	77
Reassurance	29	63
Dietary advice	43	93
Pharmacotherapy	25	55
Behavioural therapy	2	4

Discussion

IBS in primary care is a chronic disorder, with bloating and abdominal pain being the predominant diagnostic criteria for GPs and the most bothersome symptoms for patients. The GPs in this study used diagnostic criteria that coincided with the Manning criteria, but correlated poorly with the Rome ll criteria. Although diet and stress were considered important in IBS aetiology, both GPs and patients considered counselling, reassurance, and pharmacotherapy to be the key steps in IBS management. Dietary advice, although commonly given by GPs, was rarely warranted by patients. Whatever therapy is used, acceptable symptom relief should be the goal of IBS treatment.

Strenghts

Our study provides important additional insight into patients' and GPs' perceptions of IBS. Earlier reports have underlined the applicability of both the Rome and the Manning criteria in primary care. Thompson and colleagues, reported that 42% of the patients who fulfilled either the Rome or the Manning criteria for IBS were not classified as such by their GP.(1) Noticeably, other studies have indicated that GPs are not familiar with both the Rome and the Manning criteria for IBS.(7,29) Most GPs in our study, though not explicitly aware of the Rome and Manning criteria, were implicitly using the Manning criteria. The existing diagnostic criteria for IBS may be less applicable in primary care. For example, only one third of our primary care IBS patients fulfilled the strict Rome definition of more than 3 months of abdominal pain during the previous year. In fact, pain, bloating, and abdominal

distension proved to be equally important features in our patient sample. Since bloating is one of the key symptoms in the Manning criteria, two thirds of our patients did fulfil the Manning definition of IBS. That the patients did not fulfil the Rome criteria may be explained by their interpretation of symptoms: abdominal discomfort, such as bloating and abdominal distension may have been considered as a less severe form of abdominal pain. Another reason may be that many primary care IBS patients generally have milder symptomatology. Therefore the Rome II and - to a lesser extend - the Manning diagnostic criteria, both developed in a secondary care setting, may be less responsive when used in a primary care setting. A symptom-guided subclassification of IBS, as suggested by the Rome committee (5), may also be less applicable in primary care, since constipation, diarrhoea, and altered defecation were infrequently reported symptoms in our patient sample.

Comorbidity is prevalent in IBS patients: dyspepsia, psychiatric disorders, and chronic pain syndromes are frequently present. The coincidence of IBS and dyspepsia is a well-known phenomenon and some researchers consider the two conditions to be directly related.(25,26) Earlier studies have also reported an over-representation of psychological problems among IBS patients.(27) True psychiatric syndromes (depression or anxiety) occurred in only one fifth of the patients, in our primary care population. In contrast, the reported prevalence of psychiatric disorders in referred IBS patients is much higher (up to 50%).(28)

The aetiology of IBS varies widely, in the views of both patients and doctors. Many patients attribute their symptoms to either a somatic cause, stress, or food intolerance, while GPs perceive IBS aetiology to be related to stress, fibre deficiency, and disturbed motility. Evidence of an etiological role for any of these factors, however, is scarce. Nevertheless, some researchers have found that stress is a very important factor in patients' views on IBS and that the fear of cancer is an important reason for consulting a doctor.(1,10,11) One out of five IBS patients in our study reported food intolerance, which indicates the central role that diet plays for many patients in the aetiology of IBS. Although the prevalence of objectively confirmed food intolerance in (referred) IBS patients is often estimated as high as 45%, it is only 2-8%.(30,31) The benefit of exclusion diets remains therefore controversial. Nevertheless, more than half of the patients in our study had followed an exclusion diet, and the majority reported benefiting from this intervention.

In general, our patients found pharmacotherapy to be more effective than dietary interventions, while GPs considered counselling and dietary advice to be the primary factors in IBS treatment. More than half of the GPs in our study, however, started IBS management with pharmacotherapy. This is in line with earlier observations that prescription of drugs in IBS is as high as 80%.(7) Again, the evidence of the efficacy of most drug interventions in IBS is poor.(32,33,34)

Quality of life and productivity were only moderately impaired in the majority of our patients. Mean scores on the IBSQOL were comparable to those of referred IBS patients (mean score 56-92) and lower than those of patients without IBS (90-100).(24) There is evidence that compared to new patients, chronic IBS outpatients are more likely to experience the social consequences of their illness.(35) We were unable to confirm this observation with regard to the relation between duration of IBS and impaired QOL as no significant differences were found in the subgroup analyses of the "prevalent", "incident" or "latent" patients.

Conclusion

Patients and doctors in primary care generally agree on IBS symptomatology, and consider pain and bloating as its main features. Classification criteria developed in secondary care may be less applicable to primary care IBS patients. Patients see diet as a major causative factor of IBS, but regard drug therapy, more than dietary interventions, as the most effective treatment. Although GPs consider dietary advice and counselling to be the first step in IBS management, they often prescribe medication.

References

1. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. Gut 2000;46:78-82.
2. Jones R, Lydeard S. Irritable bowel syndrome in the general population. BMJ 1992;304:87-90.
3. Manning AP, Thompson WG, Heaton KW, et al. Toward positive diagnosis of the irritable bowel. Br Med J 1978;2(653):654
4. Thompson WG, Dotevall G, Drossman DA, et al. Irritable bowel syndrome: guidelines for the diagnosis. Gastroenterol Int 1989;2:92-5.
5. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. Gut 1999;45(Suppl II):II43-II47
6. Dixon-Woods M, Critchley S. Medical and lay views of irritable bowel syndrome. Fam Pract 2000;17:108-13.
7. Thompson WG, Heaton KW, Smyth CG, Smyth C. Irritable bowel syndrome: the view from general practice. Eur J Gastroenterol Hepatol 1997;9:689-92.
8. Drossman DA, Creed FH, Olden KW, Svedlund J, Toner BB, Whitehead WE. Psychological aspects of the functional gastrointestinal disorders. Gut 1999;45(Suppl II):II25-II30
9. Drossman DA. Do psychological factors define symptom severity and patient status in irritable bowel syndrome. Am J Med 1999;107:41S-50S.
10. Van der Horst HE, Van Dulmen AM, Schellevis FG, Van Eijk JThM, Fennis JFM, Bleijenberg G. Do patients with irritable bowel syndrome in primary care really differ from outpatients with irritable bowel syndrome? Gut 1997;41:669-74.
11. Kettel J, Jones R, Lydeard S. Reasons for consultation in irritable bowel syndrome: symptoms and patients characteristics. Br J Gen Pract 1992;42:459-61.
12. Talley NJ, Boyce PM, Jones M. Predictors of health care seeking for irritable bowel syndrome: a population based study. Gut 1997;41:394-8.
13. Paterson WG, Thompson WG, Vanner SJ, et al. Recommendations for the management of irritable bowel syndrome in general practice. CMAJ 1999;161(154):160.
14. De Waal M, Donker G, Van der Velden J. Spijsverteringsziekten onder de bevolking en in de huisartspraktijk. Utrecht. NIVEL/Maag Darm Lever Stichting, 1992.
15. Jansen HAM, Borghouts JAJ, Muris JWM, Metsemakers JFM, Koes BW, Knottnerus JA. Health status and management of chronic non-specific

abdominal complaints in general practice. Br J Gen Pract 2000;50(secundaire analyse chronische buikers):375-9.
16. Camilleri M. Management of irritable bowel syndrome. Gastroenterol 2000;120:652-668.
17. Jones J, Boorman J, Cann P, et al. British Society of Gastroenterology guidelines for the management of irritable bowel syndrome. Gut 2000; 47(suppl II):1-19.
18. Jones R. IBS: prime problem in primary care. Gut 2000;304:7.
19. Van Dulmen AM, Fennis JFM, Mokkink HG, Van der Velden HG, Bleijenberg G. Doctors' perception of patients' cognitions and complaints in irritable bowel syndrome at an out-patient clinic. J Psychosom Res 1994;38:581-90.
20. O'Sullivan MA, Mahmud N, Kelleher DP, Lovett E, O'Morain CA. Patients knowledge and educational needs in irritable bowel syndrome. Eur J Gastroenterol Hepatol.2000;12:39-43.
21. Classification Committee of WONA. ICHPPC-2 defined. International classification of health problems in primary care. Oxford: Oxford University Press, 1983.
22. Talley NJ, Phillips SF, Melton J, Wiltgen C, Zinmeister AR. A patient questionnaire to identify bowel disease. Ann Intern Med 1989;111:671-4.
23. Hahn BA, Kirchdoerfer LJ, Fullerton S, Mayer E. Evaluation of a new quality of life questionnaire for patients with irritable bowel syndrome. Aliment Pharmacol Ther 1997;11:547-52.
24. Hahn BA, Kirchdoerfer LJ, Fullerton S, et al. Patient-perceived severity of irritable bowel syndrome in relation to symptoms, health resource utilization and quality of life. Aliment Pharmacol Ther 1997;11:553-9.
25. Agreus L, Svaerdsudd K, Nyrén O, Tibblin G. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. Gastroenterol 1995;109:671-80.
26. Den Hartog G, Mulder CJJ, Thies JE, Wiersma TJG. The constipated stomach. An underdiagnosed problem in patients with abdominal pain? Scand J Gastroenterol 1998;33(225):41-6.
27. Donker GA, Foets M, Speeuwenberg P. Patients with irritable bowel syndrome: health status and use of health care. Br J Gen Pract 1999;49:787-92.
28. Drossman DA, Whitehead WE. AGA tecnical review irritable bowel syndrome: a technical review for practice guideline development. Gastroenterol 1997;112:2120-37.
29. Agreus L. Rome? Manning? Who Cares? Am J Gastroenterol 2000;95:2679-80.
30. Stockbrugger RW, Pace F, eds. The irritable bowel syndrome manual. London: Mosby-Wolfe, 1999.

31. Niec AM, Frankum B, Tally NJ. Are adverse food reactions linked to irritable bowel syndrome. Am J Gastroenterol 1998;93:2184-90.
32. Klein KB. Controlled treatment trials in the irritable bowel syndrome: a critique. Gastroenterol 1988;95:232-41.
33. Jailwala J, Imperiale TF, Kroenke K. Pharmocologic treatment of the irritable bowel syndrome: a systematic review of randomized, controlled trials. Ann Intern Med 2000;133:136-47.
34. Akehurst R, Kaltenhalter E. Treatment of irritable bowel syndrome; review of randomised controlled trials. Gut 2001;48:272-82.
35. Guthrie EA, Creed FH, Whorwell PJ, Tomenson B. Outpatients with irritable bowel syndrome: a comparison of first time and chronic attenders. Gut 1992;33:361-3.

Chapter 3

Determinants of consultation behaviour in primary care patients with irritable bowel syndrome

Bijkerk CJ, de Wit NJ, Hubers MAM, Muris JWM, Knottnerus JA, Hoes AW.
Submitted for publication.

Abstract

Introduction: To appropriately manage patients with irritable bowel syndrome (IBS) it is important to understand the characteristics of patients who seek medical help for IBS.

Aim: We aimed to identify determinants of consultation behaviour in primary care patients who frequently consulted for IBS in comparison to those who did not consulted frequently.

Methods: A random sample of 214 primary care IBS patients, participated in a questionnaire survey. Demographic and disease-specific characteristics and data on comorbidity, patient's cognitions and health care use were obtained and related to consultation frequency for IBS.

Results: 44% (n=94) were frequent consulters (more than once in the preceding year) (n=94) and 120 did not consult their general practitioner (GP) during the previous year or consulted the GP only once. Patients with severe IBS related abdominal pain (mean VAS score: 52.6 (scale 0-100)) and impaired health-related quality of life (mean score: 76.4 (scale 0-100)) more frequently attended their GP as did patients with distress, somatisation or depression. Independent determinants for frequent consultation were IBS according to the Rome II diagnostic criteria (OR 2.96 (95%CI: 1.19-5.98)), severity of abdominal pain (OR 1.03 (95%CI 1.02-1.95)), and referral to secondary care in the past 2 years (OR 5.70 (95%CI: 1.20-27.0)).

Conclusion: Consultation patterns for IBS in primary care vary considerably and are mainly driven by IBS symptomatology and symptom severity.

Introduction

Irritable bowel syndrome (IBS) is a functional colonic disorder characterised by abdominal pain or discomfort, altered bowel habits and bloating.(1) IBS is the most common gastrointestinal (GI) disorder in both primary and secondary care. The estimated prevalence of IBS in primary care approximates 2.5%. However, only 25% of those in the general population with IBS symptoms do seek medical advice; the vast majority of the patients is managed exclusively in primary care and less than 5% is referred to secondary care.(2) To appropriately manage IBS patients in primary care it is important to understand why patients seek help for their IBS. IBS patients who do seek help tend to make an above average use of health care resources.(3-6)

A limited number of studies on the impact of several isolated patients characteristics (including symptom severity, consultation frequency for other complaints and psychological stress) on consulting behaviour are available, but studies assessing the independent contribution of these and alternative determinants (such as patient's cognition) on consultation behaviour are lacking.(7) Moreover most studies were performed in the secondary care setting and evidence of determinants of consultation behaviour in primary care IBS patients is still scarce.(8;9) Much of the published literature on IBS may not be applicable to patients in primary care and even current guidelines are primarily based on data from studies performed in secondary and tertiary care. It is important that more research will be performed in the large group of IBS patients seen by the GP, since patients IBS patients from primary care differ considerably from those managed by hospital specialists.(10) The aim of this study was to assess determinants of consultation behaviour in primary care IBS patients who consulted frequently compared to those not frequently consulted.

Materials and methods

Study design and setting

A postal survey was sent to a random sample of patients who consulted their GP at least once in the last 2 years for IBS-related symptoms. The patients were selected from the electronic medical files in 27 practices with 43 general practitioners from the Utrecht and Maastricht academic networks in the Netherlands. We selected patients aged 18-65 years, labelled with the ICPC code D93 (Irritable bowel syndrome), or had text words in the diagnosis used by Dutch GPs to indicate IBS ('IBS', 'spastisch colon' or 'spastische darm'), during a two year period (March

2003 - March 2005). A random sample of 50% was sent a questionnaire. Non responding patients received one reminder.

Measurements

IBS symptom severity, quality of life, psychological and psychiatric morbidity, major life events, illness behaviour and patient satisfaction were measured. We assessed symptom severity by means of the IBS-SSS, a validated instrument that monitors symptoms with a VAS-score (0% to 100%).(11) We also included the IBS diagnostic Rome II criteria.(12) To measure quality of life, we used the IBS-QOL (IBS Quality of Life), a self-reporting IBS specific quality of life measurement.(13) To document psychiatric morbidity we applied the Four-Dimensional Symptom Questionnaire (4DSQ), a validated self reported questionnaire.(14) A higher score for depression, somatisation or anxiety, indicates a higher probability of a DSM-IV diagnosis for the specific subscale. A high score for distress on the 4DSQ subscale implies a high probability of surmenage or indicates that the patient is suffering from a depression or anxiety disorder. We also documented the number of major life events in the last year.

Finally, we added specific questions about patients' expectations and satisfaction with IBS-treatment and the GP's attitude, patients' ideas about the causes of IBS and about the consultation rate for other symptoms in the previous year, the use of medication for depression or anxiety, the use of fibre, and referral rate for IBS to secondary care.

Outcome

Consultation behaviour, i.e. the outcome in the study was assessed by asking the patient how many times they had consulted their GP in the last year because of their IBS. The frequencies of consultations for reasons other than IBS symptoms were registered separately. The patient population was categorised in frequent consulters (patients consulting their GP because of IBS more than once in the preceding year) and infrequent consulters (patients who did not consult their GP or consulted their GP only once because of IBS in the preceding year).

Statistical analysis

We compared the demographic and disease-specific characteristics, medical history (including psychiatric comorbidity) between frequent and infrequent consulters. Means and standard deviations (SD) were computed for continuous variables. Differences between demographic and disease specific characteristics were tested with ANOVA, or X2-test. When the expected count in the cells was less than 5 we used the Fishers' exact test. All variables that were univariately associated (p value

of <0.05) with consultation behaviour were entered in a multiple logistic regression model. Point estimates are given with corresponding 95% confidence intervals (CI). For statistical analysis SPSS for Windows 12.0.1(SPSS, Inc. Chicago, Illinois, USA) was used.

Results

Of the 537 patients invited to participate, 224 IBS patients returned the questionnaire (response rate 42%). We excluded 10 patients as the initial diagnosis of IBS had to be altered into another gastrointestinal diagnosis during follow-up (e.g. inflammatory bowel disorder, celiac disorder or colon cancer). Of the remaining 214 IBS patients, 77% were female. The mean age was 41.1 years (SD 12.6). Twenty two percent of the patients had IBS according to the Rome II criteria. Responders and non responders did not differ with respect to age and gender (data not shown).

Consultation rates

Among the 214 patients, 192 patients reported having seen their GP for IBS symptoms in the last year. Half of these patients (n=94) consulted more than once (frequent consulters). The remainder were (n= 120) were infrequent consulters and included 53 patients (24.8% of total) who did not consult their GP because of IBS in the last year. The mean number of visits for IBS in the frequent consulters was 3.9 (sd 3.1) and 0.41 (sd 0.49) in the infrequent consulters. These consulting rates did not differ with respect to gender and age (data not shown).

Determinants of consultation behaviour

Table 1 shows the univariate associations between of frequency of IBS consultations and demographic factors, IBS symptoms, psychiatric and psychosocial comorbidity and patients' cognitions.

Consultation behaviour was associated with IBS related abdominal pain, constipation and diarrhoea. Patients with IBS according to the Rome II criteria had a more than 3-fold risk of being a frequent consulter (OR 3.20 (95%CI: 1.62-6.31)). Frequent consulting was also associated with Health Related Quality of Life: the more patients suffered from IBS, they more frequently they sought help for their IBS symptoms (OR 2.65 (95%CI: 1.35-5.21)). Also psychiatric comorbidity (such as somatisation and depression) were related to consultation behaviour, as was age: patients younger than 25 years were more likely to be frequent consulters (OR 3.34 (95%CI: 1.27-8.81). In contrast, gender, the length of history of IBS, psychosocial disturbance by major life events, fear of cancer and the belief that IBS is etiological

linked to a somatic cause, psychosomatic stress, fibre deficiency, food intolerance or constipation were not predictive of consultation behaviour.

In the multivariate analysis, IBS according to the Rome II diagnostic criteria (OR 2.30 (95%CI: 1.02-5.22)), severe and moderate abdominal pain (OR 4.86, (95%CI: 1.08-21.9) and OR 5.05 (95%CI: 1.73-14.8)) and referral to secondary care in the previous 2 years for IBS (OR 4.98 (95%CI: 1.07-23.2) were independent determinants of frequent consultation for IBS during the last year.

Table 1. Demographic characteristics, abdominal symptoms, comorbidity and patients' views among patients with irritable bowel syndrome in relation to consultation behaviour in the previous year (n=214)

	Proportion of frequently (>1) consulting IBS patients		Odds Ratio (95% CI)
	N/total	%	
Age years			
<25	17/	70.8	3.34 (1.27-8.81)
25-44	37/95	38.9	0.88 (0.49-1.57)
>45*	40/95	42.1	-
Gender			
Female	74/165	44.8	1.18 (0.62-2.25)
Male*	20/49	40.8	-
Rome II IBS			
Yes	31/47	66.0	3.20 (1.62-6.31)
No*	63/167	37.7	-
Duration IBS			
0-2 years	29/61	47.5	1.21 (0.58-2.51)
2-5 years	41/97	42.3	0.98 (0.50-1.90)
> 5 years*	24/56	42.9	-
Severity of IBS abdominal pain (VAS score 0-100)			
Severe (75)	14/21	66.7	12.3 (3.53-43.1)
Moderate (25-75)	74/150	49.3	6.00 (2.39-15.1)
Mild (25)*	6/43	14.0	-
IBS abdominal pain			
Yes	59/109	54.1	2.36 (1.36-4.11)
No*	35/105	49.1	-
IBS constipation			
Yes	36/61	59.0	2.36 (1.29-4.32)
No*	58/161	37.9	-
IBS diarrhoea			
Yes	34/58	58.6	2.27 (1.23-4.19)
No*	60/156	38.5	-

* Reference category in each variable

Table 1. Continued

	Proportion of frequently (>1) consulting IBS patients		Odds Ratio (95% CI)
	N/total	%	
Quality of life (IBSQOL) score 0-100 (s.d.)			
Score <70	29/46	63.0	2.65 (1.35-5.21)
Score >=70*	65/166	39.2	-
Degree of distress			
High	13/18	72.7	4.19 (1.42-12.3)
Moderate	22/42	52.4	1.77 (0.89-3.52)
None*	59/154	38.3	-
Degree of somatisation			
High	15/23	65.2	3.85 (1.50-9.90)
Moderate	42/78	53.8	2.40 (1.32-4.34)
None*	37/113	32.7	-
Satisfied with treatment			
Yes	34/91	37.4	0.63 (0.36-1.09)
No*	60/123	48.8	-
Treated seriously by GP			
Yes	83/191	43.5	0.84 (0.35-2.00)
No*	60/123	47.8	-
Positive belief in possible treatment possibilities			
Yes	42/104	40.4	0.76 (0.44-1.30)
No*	52/110	47.3	-
Treatment for IBS			
Yes	64/124	51.6	2.13 (1.22-3.74)
No*	30/90	33.3	
Treatment with fibre (%)			
Yes	15/26	57.7	1.88 (0.82-4.32)
No*	79/188	42.0	-
Medical treatment for anxiety/depression (%)			
Yes	7/16	43.8	0.99 (0.36-2.77)
No*	87/198	43.9	-
Referral (%)			
Yes	11/14	78.6	5.17 (1.40-19.1)
No*	83/200	41.5	-

* Reference category in each variable

Discussion

Our study demonstrates that IBS patients in primary care frequently consult their GP because of their IBS symptoms. Although relief from abdominal pain with bowel movements and change in frequent bowel movements and psychiatric comorbidity

/psychological disturbances were associated with consultation behaviour, these associations disappeared after adjustment for confounding. Only IBS according to the Rome II diagnostic criteria, severity of abdominal pain and referral for IBS in the past 2 years were independent determinants of consultation frequency

All crude (i.e. not adjusted for confounding) results harmonize well with other studies.(15-17) There is growing evidence that psychosocial disturbances are linked to health care seeking in IBS.(18) However, we found psychiatric comorbidity not to be significantly associated with consultation behaviour in primary care IBS patients after controlling for confounding.

We showed that although patients' views on aetiology and management of IBS were not associated with consultation behaviour, more frequent consulters were less satisfied with the management of their bowel problems. This is in line with an earlier study which reportedthat a positive physician-patient interaction may be related to reduced use of ambulatory health services by patients with IBS.(19) Other studies demonstrated that IBS patients who feared that their symptoms indicated severe bowel disease hada greater likelihood of seeking medical advice than those who did not.(20) Our results confirm the study by Van der Horst et al.(10) which demonstrated that primary care patients more frequently attributed their bowel problems to factors like stress and eating habits, compared to outpatient with IBS who more often attribute their bowel symptoms to a organic problem. This could indicate that distress contributes to anxiety, depression and somatisation in IBS patients.It has been suggested, however, that somatisation does not predict the number of health care visits, but that physicians possibly mediate the relationship between somatisation and health care costs.(21-23) Others found that comorbid symptoms were associated with reduced global health status and increased health-care seeking.(24)

Strengths and limitations

We included a broad spectrum of IBS patients with a wide spectrum of patient- and disease related factors to asses their crude and, importantly, also independent impact on consultation behaviour. To our knowledge, this is the first study that assessed the relationship between patients' views of IBS patients in primary care and consultation behaviour. The main limitation of our study is that we could not retrieve additional information on the selected and approached patients not responding to the mailing. Only 41% of the patients invited for this survey completed the questionnaire. This is probably explained by the fact that the majority of the non-responders had no actual complaints in the past month and did not consult their GP in the past year.

Conclusion

Consultation behaviour is mainly driven by IBS symptomatology and severity of IBS related abdominal pain, rather than by the nature of IBS, Health Related Quality of Life and psychological distress. These findings have important potential implications for the management of frequent attendees for IBS in primary care. Further studies are necessary to evaluate interventions to optimize management of frequently consulting IBS patients in primary care.

References

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006 Apr;130(5):1480-91.
2. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. Gut 2000 Jan;46(1):78-82.
3. Levy RL, Von Korff M, Whitehead WE, Stang P, Saunders K, Jhingran P, et al. Costs of care for irritable bowel syndrome patients in a health maintenance organization. Am J Gastroenterol 2001 Nov;96(11):3122-9.
4. Sandler RS, Drossman DA, Nathan HP, McKee DC. Symptom complaints and health care seeking behavior in subjects with bowel dysfunction. Gastroenterology 1984 Aug;87(2):314-8.
5. Drossman DA. Do psychosocial factors define symptom severity and patient status in irritable bowel syndrome? Am J Med 1999 Nov 8;107(5A):41S-50S.
6. Levy RL, Whitehead WE, Von Korff MR, Feld AD. Intergenerational transmission of gastrointestinal illness behavior. Am J Gastroenterol 2000 Feb;95(2):451-6.
7. Bijkerk CJ, de Wit NJ, Stalman WA, Knottnerus JA, Hoes AW, Muris JW. Irritable bowel syndrome in primary care: the patients' and doctors' views on symptoms, etiology and management. Can J Gastroenterol 2003 Jun;17(6):363-8.
8. Paterson WG, Thompson WG, Vanner SJ, Faloon TR, Rosser WW, Birtwhistle RW, et al. Recommendations for the management of irritable bowel syndrome in family practice. IBS Consensus Conference Participants. CMAJ 1999 Jul 27;161(2):154-60.
9. Boukes FS, van der Horst HE, Assendelft WJ. (Summary of The Dutch College of General Practitioners' 'Irritable bowel syndrome' standard). Ned Tijdschr Geneeskd 2002 Apr 27;146(17):799-802.
10. van der Horst HE, van Dulmen AM, Schellevis FG, van Eijk JT, Fennis JF, Bleijenberg G. Do patients with irritable bowel syndrome in primary care really differ from outpatients with irritable bowel syndrome? Gut 1997 Nov;41(5):669-74.
11. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997 Apr;11(2):395-402.
12. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. Gut 1999 Sep;45 Suppl 2:II43-II47.

13. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci 1998 Feb;43(2):400-11.
14. Terluin B, van Marwijk HW, Ader HJ, de Vet HC, Penninx BW, Hermens ML, et al. The Four-Dimensional Symptom Questionnaire (4DSQ): a validation study of a multidimensional self-report questionnaire to assess distress, depression, anxiety and somatization. BMC Psychiatry 2006;6:34.
15. Koloski NA, Talley NJ, Huskic SS, Boyce PM. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia. Aliment Pharmacol Ther 2003 Mar 15;17(6):841-51.
16. Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC, et al. Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. Gastroenterology 1988 Sep;95(3):701-8.
17. Williams RE, Black CL, Kim HY, Andrews EB, Mangel AW, Buda JJ, et al. Determinants of healthcare-seeking behaviour among subjects with irritable bowel syndrome. Aliment Pharmacol Ther 2006 Jun 1;23(11):1667-75.
18. Vandvik PO, Wilhelmsen I, Ihlebaek C, Farup PG. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. Aliment Pharmacol Ther 2004 Nov 15;20(10):1195-203.
19. Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long-term prognosis and the physician-patient interaction. Ann Intern Med 1995 Jan 15;122(2):107-12.
20. Gaynes BN, Drossman DA. The role of psychosocial factors in irritable bowel syndrome. Baillieres Best Pract Res Clin Gastroenterol 1999 Oct;13(3):437-52.
21. Koloski NA, Talley NJ, Huskic SS, Boyce PM. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia. Aliment Pharmacol Ther 2003 Mar 15;17(6):841-51.
22. Koloski NA, Talley NJ, Boyce PM. Epidemiology and health care seeking in the functional GI disorders: a population-based study. Am J Gastroenterol 2002 Sep;97(9):2290-9.
23. Locke GR, III, Weaver AL, Melton LJ, III, Talley NJ. Psychosocial factors are linked to functional gastrointestinal disorders: a population based nested case-control study. Am J Gastroenterol 2004 Feb;99(2):350-7.
24. Vandvik PO, Lydersen S, Farup PG. Prevalence, comorbidity and impact of irritable bowel syndrome in Norway. Scand J Gastroenterol 2006 Jun;41(6):650-6.

Chapter 4

The historical relation of irritable bowel syndrome with comorbidity

Bijkerk CJ, Hoes AW, Vleugel F, Hak E, de Wit NJ.
Manuscript in preparation for submission.

Abstract

Introduction: Irritable bowel syndrome (IBS) has a complex multifactorial background. Although a high prevalence of comorbidity has been reported, the historical relationship between IBS and comorbidity is unclear.

Aims: To assess the historical perspective of clusters of somatic, functional, psychiatric and psychosocial comorbidity over a 10-year time period (1996-2005) in IBS patients and matched controls.

Methods: Retrospective follow-up study in a large academic primary care network, comparing a random sample of 371 IBS patients with 411 matched non-IBS controls exploring the electronic medical files from the practices.

Results: In IBS patients (68% females, mean age 40 (SD 13)), the prevalence of somatic disorders was 259‰, functional, psychiatric and psychosocial problems were less common with a prevalence of 42‰, 60‰ and 81‰, respectively. Comorbidity was more frequently registered for all clusters compared to controls. The highest odds ratios were found for functional disorders among IBS patients (OR 6.64 (95%CI: 3.21-13.7)). Somatic disorders had a high prevalence in patients with a short history of IBS (<2 years) and peaked six-fold in the year of IBS diagnosis. The prevalence of functional, psychiatric and psychosocial problems doubled in the year of the diagnosis of IBS but remained at that level in the years after the diagnosis.

Conclusion: Irritable bowel syndrome is associated with a high prevalence of comorbidity. Somatic comorbidity is a common feature in the year of IBS diagnosis and drops afterwards, while functional and psychiatric disorders remain highly prevalent. Patients with such comorbidities might need targeted treatment approaches.

Introduction

Irritable bowel syndrome (IBS) is a common functional bowel disorder in which abdominal pain is associated with features of disordered defecation.(1;2) IBS is a chronic condition with recurrent symptoms and has a complex multi-factorial background, in which altered motility, pain perception, infections and psychosocial factors are all suggested to play a role. On average only 25% of those with IBS seek medical attention.(2-4) Consulting IBS patients were reported to have an increased prevalence of somatic, functional and psychiatric comorbidity and a higher burden of major life events compared to IBS patients not seeking medical attention. In a systematic review Whitehead et al. describe IBS as a distinct disorder with several potential explanatory models. A dual-aetiology hypothesis is suggested, dividing IBS patients in two groups according to comorbidity patterns.(5) In patients with considerable somatic comorbid complaints and disease IBS is supposed to have a predominantly psychological origin, while in those with few somatic complaints IBS is considered to have a predominantly biological aetiology.(6)

Although the increased prevalence of comorbidity in IBS patients has been firmly established in cross-sectional research, the longitudinal relationship between IBS and comorbidity is largely unknown.(7-9) Detailed assessment of preceding and subsequent comorbidity patterns might reveal subcategories of IBS patients with distinct characteristics and prognosis, potentially facilitating more accurate, individualised management in an early stage. However, so far no studies explored the temporal relation between different types of comorbidity and IBS.

We assessed the prevalence of comorbidity in IBS in a large primary care database, and analysed the historical relation of IBS and somatic, functional, psychiatric and psychosocial comorbidity over a 10-year time period.

Methods

Setting

Data for this retrospective follow-up study were extracted from the Primary Care Network Utrecht (PCNU), a large primary care database affiliated with the University Medical Center Utrecht. The PCNU database contains information about the presented health problems and GP consultations of 41,072 primary care patients from 27 general practitioners. Patients in the PCNU database are representative of the Dutch population at large.(10) Health problems have been systematically coded in the database for 15 years, using the International Classification of Primary Care (ICPC) system.(11)

Patients and controls

Patients with IBS that were diagnosed in the network in the period 2004-2005 were selected by searching the electronic medical files (EMF) for the ICPC code D93 (irritable bowel syndrome), or diagnoses indicating IBS ('IBS', 'spastisch colon' and 'spastische darm'). In the network we randomly selected an equal number of non-IBS controls, matched for 5 year age category, sex and primary care practice.

Comorbidity data

For each IBS patient the year of the diagnosis was registered. Two authors (FV, RB) manually searched the electronic medical patient files of all the IBS patients and controls, and identified and categorised for each patient all registered comorbidity between January 1996 and December 2005. Comorbidity was clustered in 4 sub-groups:(12)

1. Somatic diseases and symptom diagnoses (i.e. known organic cause).
2. Functional syndromes (without a known organic cause) (e.g. fibromyalgia, migraine).
3. Psychiatric disorders (DSM IV defined).
4. Psycho-social problems (life events/problems in social, environment, personal atmosphere without a DSM IV diagnosis).

Statistical analysis

All comorbid diagnoses were only counted once, also in case of chronic disease. First we calculated the average annual prevalence of comorbidity per year over the 3 years after the IBS diagnosis, and reported the prevalence of the separate diagnoses as well as the clustered comorbidity subgroups (somatic, functional, psychiatric and psychosocial problems). Similarly, we calculated the prevalence of comorbidity among control patients over a comparable 3 year time period, (2003-2005).

Next, we compared the prevalence of comorbidity between IBS patients with a short (<2 years), intermediate (2-5 years) and a long (>5 years) disease history. Finally we compared the annual prevalence of comorbidity clusters in the years before, the year of the IBS diagnosis and the years after the diagnosis of IBS. Because the observation periods before and after the diagnosis varied per patient we calculated the number of observation years for each individual IBS patient, and reported the prevalence of comorbidity as the total number of diagnoses per comorbidity cluster per observation year. The proportional differences between IBS patients and control patients in the outcomes were assessed using chi-square and logistic regression models to estimate p-values and odds ratio's with 95% confidence intervals. Statistical analyses were performed using SPSS for Windows 12.0.1 (SPSS, Inc. Chicago, Illinois, USA).

Results

Patients

Over the two year period we identified 395 patients with a diagnosis of IBS in the PCNU network. Of these 14 had to be excluded because they were reclassified during follow-up consultation as having inflammatory bowel disease (IBD), colon cancer or other organic bowel disease. In addition, 10 patients were excluded because follow up data were missing. We randomly extracted 421 matched control subjects from the PCNU database, of who 10 had to be excluded because they had a diagnosis of IBS. The remaining 371 IBS patients and 411 controls were eligible for the analysis. Among the IBS patients there was a female predominance (68%) and the mean age was 40 years (SD 13). In the majority of patients, IBS was diagnosed during midlife; only 14% of the patients were older than 55 years of age at the time of diagnosis. For IBS patients the mean observation period after the diagnosis was 2.8 years (SD 2.5). The average annual consultation rate in primary care during the 10 year observation period was 5.4 (SD 3.6) for IBS patients and 2.8 (SD 2.6) for control patients.

Prevalence of comorbidity

Almost all individual comorbid somatic diseases and symptoms were more common among IBS patients than among controls, except for hypertension, diabetes mellitus and thyroid disease (table 1). Locomotor tract problems such as low back-pain, neck pain and chest pain were 3-4 times more frequent among IBS patients, gastroenterological symptoms were 4 (gastric pain) to 12 (dyspepsia, nausea) times as common. In addition, the reported prevalence of all registered functional disorders, psychiatric diseases and psychosocial problems was also higher among IBS patients compared to controls. Rheumatoid arthritis, temporomandibular disorder, chronic pelvic pain, chronic fatigue syndrome, whiplash, schizophrenia and sexual/physical abuse were rare in both IBS patients and controls.

After clustering, all four comorbidity subgroups were more frequent among IBS patients than in controls (table 2). The same was true for all somatic disorder subgroups, except for infectious disease. Functional disorders were six times more common among IBS patients.

Comorbidity in relation to IBS disease history

The prevalence of somatic comorbidity was highest among patients with a recent (less than 2 years ago) diagnosis of IBS (table 3). This was particularly true for the subgroups chronic disease and locomotor disorders. For psychological comorbidity such a temporal relation was less pronounced, but the prevalence of functional

disorders and psychosocial problems was highest among patients with an intermediate disease history (2-5 years).

Table 1. Comorbidity in irritable bowel syndrome patients (n=371) and controls (n=411); total number of ICPC diagnosis (N) and prevalence per 1000 observation years (2003-2005)

		IBS patients (1133 patient observation years)		Controls (1288 patient observation years)			
ICPC		N	‰	N	‰	OR	(95% CI)
	Somatic disorder						
R95,96	Asthma/COPD/emphysema	60	58	16	13	4.76	(2.69-8.43)
T85,86	Thyroid disease	5	5	6	5	0.92	(0.28-3.08)
T90	Diabetes mellitus	13	13	13	11	1.11	(0.51-2.43)
K86	Hypertension	37	36	36	29	1.15	(0.71-1.86)
L88	Rheumatoid arthritis	2	2	0	0	-	
D02	Gastric pain	95	92	27	2	4.90	(3.11-7.71)
D03	Heart burn	37	36	7	6	6.39	(2.81-14.5)
D09	Nausea	32	31	3	2	12.8	(3.90-42.8)
D84	Reflux oesofagitis (GORD)	26	75	9	7	3.37	(1.56-7.28)
D85	Peptic ulcer disease	42	41	0	0	-	
D87	Dyspepsia	21	20	6	5	12.3	(2.86-52.7)
L01	Neck pain	108	105	38	31	4.03	(2.70-6.03)
L03	Low back pain	189	184	80	65	4.30	(3.13-5.91)
L04	Chest pain/Tietze's syndrome	115	112	34	28	4.98	(3.29-7.54)
L08	Shoulder pain	99	96	47	38	2.92	(1.93-4.13)
L09	Arm pain (hand, wrist)	98	95	38	31	3.86	(2.54-5.85)
L13	Hip pain	36	35	9	7	4.80	(2.28-10.1)
L14	Leg pain (toe, foot, ankle)	65	63	30	24	2.70	(1.71-4.27)
L15	Knee pain	61	59	27	22	2.80	(1.74-4.51)
R05	Cough	108	105	50	41	2.97	(2.05-4.30)
R21	Sore throat	86	84	26	21	4.47	(2.81-7.11)
U71	Urinary tract infection	11	11	3	2	4.16	(1.15-15.0)
	Functional disorder						
A04	Fatigue	116	104	36	28	4.74	(3.16-7.11)
D82	Tempero manibular dysfunction	6	6	2	1	3.36	(0.67-16.8)
K04	Palpitations/aware of heartbeat	37	36	9	7	4.95	(2.35-10.4)
L18	Fibromyalgia	19	18	2	1	22.1	(2.95-166)
L99	Whiplash	4	3	0	0	-	
N01	Headache	122	119	30	24	6.22	(4.05-9.57)
N17	Dizziness	72	70	14	11	6.83	(3.78-12.3)
N89	Migraine	18	18	3	2	6.94	(2.03-23.7)
R98	Hyperventilation	47	46	1	1	9.79	(4.14-23.2)
X01	Chronic pelvic pain	1	1	2	1	0.55	(0.05-6.12)

Table 1. Continued

		IBS patients (1133 patient observation years)		Controls (1288 patient observation years)			
ICPC		N	‰	N	‰	OR	(95% CI)
	Psychiatric disorder						
P06	Sleeping problems	48	47	9	7	6.64	(3.21-13.7)
P01,02,74	Anxiety disorder	30	29	7	6	5.08	(2.20-11.7)
P75	Somatisation disorder	6	6	1	1	6.74	(0.81-56.2)
P78	Surmenage/burned-out	59	57	25	20	2.92	(1.79-4.77)
P03,97	Depression	41	40	16	12	3.07	(1.69-5.57)
P72	Schizophrenia	0	0	1	1	-	
	Psychosocial problem						
Z05,06	Work problems/fired	39	38	11	9	4.27	(2.15-8.47)
Z12	Relationship problems	31	30	14	11	2.59	(1.35-4.94)
Z15	Morning/death of relative	22	21	7	6	3.64	(1.54-8.62)
Z25	Sexual/physical abuse	5	5	4	3	1.39	(0.37-5.22)

Table 2. Comorbidity clusters in irritable bowel syndrome patients (n=371) and controls (N=411) total number of ICPC diagnosis (N) and prevalence per 1000 observation years (2003-2005)

	IBS patients (1133 patient observation years)		Controls (1288 patient observation years)		OR	(95%CI)
	N	‰	N	‰		
Somatic disorder	294	259	268	217	2.04	(1.48-2.81)
Chronic disease	95	84	77	62	1.49	(1.06-2.10)
Gastrointestinal disorder	68	60	35	28	2.41	(1.56-3.72)
Locomotor disorder	189	167	168	136	1.50	(1.13-1.99)
Infectious disease	75	66	64	52	1.37	(0.95-1.99)
Functional disorder	48	42	9	7	6.64	(3.21-13.7)
Psychiatric disorder	68	60	41	33	2.03	(1.34-3.07)
Psychosocial problem	92	81	57	46	2.05	(1.42-2.95)

Table 3. Prevalence of comorbidity clusters in irritable bowel syndrome patients with a short (<2 years) intermediate (2-5 years) and long (> 5 years) IBS disease history (n=57); total number of ICPC diagnosis and prevalence per 1000 observation years

	IBS disease history						
	< 2 years (N= 148 patients, 195 observation years)		2- 5 years (N=166 patients, 485 observation years)		> 5 years (N= 57 patients, 453 observation years)		P-values
	N	‰	N	‰	N	‰	
Somatic disorder	89	456	150	309	55	121	< 0.001
Chronic disease	27	138	38	78	30	66	< 0.001
Gastrointestinal disorder	9	46	29	60	30	66	< 0.001
Locomotor disorder	46	236	96	198	47	104	< 0.001
Infectious disease	17	87	32	66	26	57	<0.001
Functional disorder	9	46	26	54	13	29	0.002
Psychiatric disorder	17	87	28	58	23	51	< 0.001
Psychosocial problem	14	72	49	101	29	64	< 0.001

Comorbidity before, during and after the diagnosis of IBS

The average annual prevalence of the different types of comorbidity before, during and after the year in which IBS was diagnosed is shown in table 4. For almost all comorbidity clusters the annual prevalence was highest in the year of the IBS diagnosis, and lowest in the period before the diagnosis of IBS. The prevalence of somatic comorbidity increased six-fold in the year of the IBS diagnosis, but dropped considerably in the years thereafter. This was also true for most subgroups of somatic comorbidity, except for infectious disease. The prevalence of functional, psychiatric and psychosocial disorders doubled in the year the diagnosis IBS was set, but remained at that higher level in the following years.

Table 4. The prevalence of comorbidity clusters among irritable bowel syndrome patients (n=371) before, during and after the year of diagnosis absolute number of ICPC diagnoses and prevalence per 1000 observation years

	Before the year of IBS diagnosis (2485 patient observation years)		During the year of the IBS diagnosis (371 patient observation years)		After the year of the IBS diagnosis (853 patient observation years)		P-values
	N	‰	N	‰	N	‰	
Somatic disorder	292	117	269	725	294	345	0.05
Chronic disease	63	25	54	145	95	111	<0.001
Gastrointestinal disorder	67	26	44	119	68	80	0.03
Locomotor disorder	223	90	116	312	189	222	<0.001
Infectious disease	90	36	32	86	75	88	<0.001
Functional disorder	49	20	26	70	48	56	0.001
Psychiatric disorder	86	35	29	78	68	80	<0.001
Psychosocial problem	92	37	32	86	92	108	<0.001

Discussion

In this retrospective follow-up study we analysed the prevalence of comorbidity in IBS patients in primary care in a historical perspective of 10 years. We were able to confirm the reported increased prevalence of all types of comorbidity in IBS patients. Functional disorders were six times more common among IBS patients compared to age, sex and GP practice matched controls, while somatic, psychiatric and psychosocial problems occurred twice as frequently. The historical analyses demonstrated a clear and consistent trend: for all comorbidity subcategories the prevalence of comorbidity is lowest in the years before, and highest during the year in which IBS is diagnosed. Somatic comorbidity peaks in the year of the IBS diagnosis, but drops again in the following years. In contrast, the prevalence of psychosocial, functional and psychiatric comorbidity remains high in the years after the diagnosis.

Our longitudinal analysis does not allow causal interpretation. However, our results demonstrate that before patients are diagnosed with IBS, the average prevalence of comorbidity is quite comparable to the prevalence in a random sample of matched patients from primary care. Somatic comorbidity increases dramatically in the period in which IBS is diagnosed, possibly due to an increased consultation frequency and/or an elevated alertness for physical symptoms. This could at least partly be attributable to increased anxiety or stress as a consequence of psychosocial problems; as both these types of comorbidity are clearly increased. After the IBS diagnosis is set, the prevalence of psychiatric and psychosocial comorbidity remains

increased, while that of somatic comorbidity drops substantially. This suggests that IBS is triggered by psychiatric factors or major life events, and is not a "side-effect" of frequent consultations because of somatic complaints.

The reported frequencies of comorbid somatic and psychiatric disorders among IBS patients is in line with previous studies.(13-17) In our primary care population we could not confirm the relationship between IBS and sexual or physical abuse reported earlier in tertiary care patients.(18) The high prevalence of functional comorbidity in IBS patients might in fact reflect a somatisation disorder as a common feature, which may present itself in various distinct functional syndromes.

Whitehead suggested that a high prevalence of comorbidity discriminates IBS patients with a predominantly psychological aetiology from those with a biological genesis.(5) Our results confirm a generally increased prevalence of comorbidity at the time of the diagnosis, but during follow-up only the increased prevalence of psychological comorbidity persisted.

The UPCN network population is representative for the Dutch population, and GPs in the network have a longstanding experience in electronic registration and ICPC coding. To reach optimal validity we manually screened all electronic medical files of IBS – and control patients for comorbidity. Retrospective network searches have several inherent limitations; e.g. the analysis was restricted to presented and reported comorbidity and in some consultations not all comorbidity may have been registered.

We conclude that the prevalence of comorbidity increases around the time that IBS is diagnosed, but is not elevated before the diagnosis. In contrast to somatic comorbidity the prevalence of psychosocial comorbidity remains increased after the diagnosis of IBS. These patients might need targeted (i.e. psychological) treatment approaches.

References

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006 Apr;130(5):1480-91.
2. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. Gut 2000 Jan;46(1):78-82.
3. Koloski NA, Talley NJ, Boyce PM. Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. Am J Gastroenterol 2001 May;96(5):1340-9.
4. Bijkerk CJ, de Wit NJ, Stalman WA, Knottnerus JA, Hoes AW, Muris JW. Irritable bowel syndrome in primary care: the patients' and doctors' views on symptoms, etiology and management. Can J Gastroenterol 2003 Jun;17(6):363-8.
5. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? Gastroenterology 2002 Apr;122(4):1140-56.
6. Levy RL, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, et al. Psychosocial aspects of the functional gastrointestinal disorders. Gastroenterology 2006 Apr;130(5):1447-58.
7. Lydiard RB. Anxiety and the irritable bowel syndrome: psychiatric, medical, or both? J Clin Psychiatry 1997;58 Suppl 3:51-8.
8. Lydiard RB. Irritable bowel syndrome, anxiety, and depression: what are the links? J Clin Psychiatry 2001;62 Suppl 8:38-45.
9. Vandvik PO, Lydersen S, Farup PG. Prevalence, comorbidity and impact of irritable bowel syndrome in Norway. Scand J Gastroenterol 2006 Jun;41(6):650-6.
10. Hak E, Rovers MM, Kuyvenhoven MM, Schellevis FG, Verheij TJ. Incidence of GP-diagnosed respiratory tract infections according to age, gender and high-risk co-morbidity: the Second Dutch National Survey of General Practice. Fam Pract 2006 Jun;23(3):291-4.
11. Classification Committee of WONCA. ICHPPC-2 defined. International classification of health problems in primary care. Oxford: Oxford University Press; 1983.
12. Whitehead WE, Palsson OS, Levy RR, Feld AD, Turner M, VON KM. Comorbidity in Irritable Bowel Syndrome. Am J Gastroenterol 2007 Sep 27.

13. Vandvik PO, Wilhelmsen I, Ihlebaek C, Farup PG. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. Aliment Pharmacol Ther 2004 Nov 15;20(10):1195-203.
14. Huitema H.O, Buntinx E, Muris J.W., Metsemakers JF, Knottnerus JA. Comorbidity of chronic gastro-intestinal disorders: a cross-sectional analysis in a large general practice population in the Netherlands. Arch Public Health 2000;58:213-31.
15. Nimnuan C, Rabe-Hesketh S, Wessely S, Hotopf M. How many functional somatic syndromes? J Psychosom Res 2001 Oct;51(4):549-57.
16. Drossman DA, Creed FH, Olden KW, Svedlund J, Toner BB, Whitehead WE. Psychosocial aspects of the functional gastrointestinal disorders. Gut 1999 Sep;45 Suppl 2:II25-II30.
17. Jones R, Latinovic R, Charlton J, Gulliford M. Physical and psychological co-morbidity in irritable bowel syndrome: a matched cohort study using the General Practice Research Database. Aliment Pharmacol Ther 2006 Sep 1;24(5):879-86.
18. Drossman DA, Leserman J, Nachman G, Li ZM, Gluck H, Toomey TC, et al. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. Ann Intern Med 1990 Dec 1;113(11):828-33.

Chapter 5

Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics

Published as: Bijkerk CJ, de Wit NJ, Muris JWM, Jones RH, Knottnerus JA, Hoes AW. Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological properties. *Am J Gastroenterol* 2003;98:122-7.

Abstract

Background: Although there is growing interest in irritable bowel syndrome (IBS) research, there is as yet no consensus regarding the preferred outcome measure.
Aims: To evaluate and compare the validity and appropriateness of available IBS outcome measures.
Methods: IBS symptom and IBS health-related quality of life (HRQOL) scales were identified through a literature search. In a panel evaluation, six reviewers independently rated the scales according to predetermined psychometric and methodological validation criteria.
Results: Five IBS symptom scales and five IBS health-realted quality of life (HRQOL) instruments were identified. Two of the symptom scales were rated adequate. The Adequate Relief scale scored best. This scale demonstrates responsiveness, face-, and construct validity, and its score was considered easy to interpret and appropriate for use. According to the reviewers, the IBS Severity Scoring System performed well with regard to psychometric capacities, but its practical utility was considered debatable. The properties of the other three symptom scales were suboptimal. The practical utility of the five IBS-specific HRQOL scales was considered poor. However, the reviewers agreed that, at present, the IBS Quality of Life measurement is the best choice, since it has been the most extensively validated and shows appropriate psychometric quality. *Conclusions:* The Adequate Relief question is the measure of first choice when assessing global symptomatology as an outcome in IBS studies. For a more detailed IBS symptom assessment the IBS Severity Scoring System is preferable. Finally, the IBS Quality of Life measurement scale can be used to establish changes in health-related quality of life.

Introduction

There is a growing interest in the outcome measure of use in irritable bowel syndrome (IBS) research.(1) As a primary outcome measure, this type of research relies on either a "clinically significant" change on a symptom scale or a patient-defined judgement of improvement.(2) Outcome in IBS treatment trials can be assessed by using either a global scale, by a validated symptom questionnaire, or a quality of life (QOL) instrument.(3) Global scales are the most frequently used and usually include a single question (e.g. "rate the severity of your most bothersome symptom") on symptom severity or symptom change as rated by the patient. Specific measuring instruments, like a validated symptom questionnaire, describe changes in various symptoms in more detail, but may be complex to administer and may miss unexpected effects.(4) The measuring instruments to assess health-related quality of life (HRQOL), may either be generic or disease-specific. Today, generic QOL questionnaires such as the sickness impact profile (SIP)(5), the psychological general well-being (PGWB) index,(6) and the short form 36 (SF36)(7) are widely used in controlled IBS trials.(8) Although these scales allow comparisons with other disease groups, digestive symptoms have a low weight. As a result, the disease-specific impact of IBS may be underestimated. In contrast, IBS-specific instruments are able to detect the most relevant disease- related health consequences. Researchers now agree that outcome assessment in IBS treatment trials should include an HRQOL instrument, since IBS clearly influences general well-being and health perception.(9) Moreover, a disease-specific HRQOL measurement is preferred above generic QOL instruments, because it is more sensitive to patients' health-related consequences and concerns.(10)

A wide range of (frequently non-standardised) outcome measures has been used in past IBS treatment trials.(11) At present, there is still no consensus regarding the most appropriate outcome scale to use.(2) Since this makes comparison of such trials very difficult, it is of major importance that researchers agree on the preferred type of outcome measure for future IBS trials.

Furthermore, it is recognised that a validated instrument should determine the principal endpoint in outcome assessment.(2) Moreover quality assessment of outcome scales should include validity, reliability, and responsiveness.(10) From a practical point of view, these scales should also have practical utility and be appropriate for use.(4,12) Studies assessing both psychometric and methodological qualities of IBS outcome measurements, however, are scarce.(13) The aim of this study, therefore, was to evaluate and compare the psychometric and methodological quality of available IBS outcome measures.

Methods

IBS symptom scales and HRQOL measures were identified by means of a literature search using the MEDLINE database. The search terms included "outcome measurement and IBS", "questionnaire and IBS", and "quality of life and IBS". Reference lists of relevant citations were also screened in order to identify any study that might have been overlooked. A manual search of proceedings and abstracts of recent congresses on the subject and direct inquiry of IBS experts with regard to additional IBS outcome instruments completed the search. Non-IBS-specific symptom questionnaires and QOL instruments were excluded.

In the next part, six reviewers (RB, NdW, JM, RJ, AK and AH) independently scored the identified IBS outcome measures by rating methodological and psychometric quality according to 12 different assessment criteria. Eight essential psychometric criteria were derived from the available guidelines on quality assessment in validation trials.(10)(12)(14) Four methodological assessment criteria were included, to establish more accurately the appropriateness of use (Table 1). Reviewers scored + when the assessment criterion was completely fulfilled, ± when it was partly fulfilled, and - when it was not met or when information was not provided. After this first assessment round, each reviewer received feedback with regard to any major discrepancies with the rest of the review team (more than two fully discordant reviewers). He was then given the opportunity to reconsider his score. Consensus on an item was defined as agreement between at least five of the six reviewers. If less than five reviewers agreed, the criterion was assessed as ±.

Table 1. Criteria for assessment of symptom questionnaires and HRQOL.(10,12)

Assesment		Score
A	Does the measure have satisfactory reliability (internal consistency)? (e.g., defined by Cronbachs alpha)	
B	Is the measure sensitive to change (responsiveness)?	
C	Does the measure measure what is supposed to measure (face validity)?	
D	Does the measure sample the domain of interest comprehensively content validity?	
E	Is the measure compared with other measures and is the relation between measure and patient characteristics defined (construct validity)?	
F	Is the outcome interpretable, are changes in score related to marker states that are familiar and meaningful to clinicians?	
G	Is the measure easy to administer, showing practical utility?	
H	Is the measure appropriate for use?	
I	Are the variables clearly and unambiguously defined?	
J	Are criteria for in- and exclusion reported?	
K	Is the population in the validation report described?	
L	Has the measure been used in a primary care population?	

Results

Symptom scales

Five IBS symptom scales were identified. The first outcome measure, the Adequate Relief (AR) addresses symptom improvement in IBS treatment with a single question ("Did you have relief of IBS-related abdominal pain or discomfort?") scored on a dichotomous scale.(15) This instrument was validated in an IBS clinical trial involving 370 diarrhoea predominant IBS patients fulfilling the Rome diagnostic criteria for IBS.(16,17) The second scale, the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) was developed and tested by Francis et al.(18) in a therapy-resistant, referred population evaluating the efficacy of hypnotherapy. The IBS-SSS is divided into two parts: part one includes the actual severity score, while part two provides additional information on items not in included in the severity score (e.g., bowel frequency, stool consistency, and the impact of symptoms on productivity). The score of this system is based on five items (severity, duration of pain, abdominal distension, bowel satisfaction, and interference with life in

general) and uses visual analogue scales. Patients can be categorised as having mild (75-175), moderate (175-300), or severe (>300) IBS. The Gastrointestinal Symptom Rating Scale (GSRS) was primarily developed for dyspeptic patients, but was validated in patients with upper abdominal complaints and IBS.(19,20) It was originally developed for administration by an interviewer, but can also be used for self-assessment. The original measure was recently modified by the addition of symptoms characteristic of IBS according to the Rome criteria and evaluated in a "mock trial" including 234 patients with moderate to severe IBS.(17) Outcome is measured on 15 items using a seven-point Likert scale (range: from no to very severe discomfort) and on 5 different subitems (bloating, diarrhoea, constipation, pain, and satiety). The Functional Bowel Disorder Severity Index) (FBDSI), developed by Drossman et al.(21), was the fourth measure we screened. It has three key items: severity of current pain (measured on a visual analogue scale), diagnosis of chronic functional abdominal pain, and number of physician visits over the previous six months. Patients can be stratified according to their total scores into mild (<37), moderate (37-110), or severe (>110). This index was evaluated in two clinical studies.(22,23) The fifth measure, the IBS symptom questionnaire (IBS-Q), was developed to assess the effect of treatment in clinical IBS trials and includes the Rome diagnostic criteria for IBS. It was used in studies in Europe, North America, Australia, Middle East, and Japan and validated against a global symptom assessment procedure.(24)

Quality of life instruments

Five IBS-specific HRQOL instruments were identified during the literature search. The first was the Irritable Bowel Syndrome Quality of Life measurement (IBS-QOL), comprises a 34-item instrument developed by Patrick et al.(25) It is scored using five point Likert scales with scores summed in eight subscales. In a later study using this instrument, gastroenterologists from different countries performed the item selection, and validation evaluation was conducted using female patients enrolled in a multicentre treatment trial for functional bowel disorders.(26) The second QOL instrument, the Irritable Bowel Syndrome Quality of Life Questionnaire (IBSQOL), was developed by Hahn et al.(27) It includes 30 items scored using a five- or six-point Likert scale in nine subscales.(28) The instrument was tested on referred IBS patients in the UK and US.(29) The Digestive Health Status Instrument (DHSI), developed by Shaw et al.,(30) was the third scale we evaluated. The disease-specific part of this instrument includes both the Rome criteria for dyspepsia and the Manning and Rome criteria for IBS. The DHSI comprises 34 items in five different symptom subscales (IBS diarrhoea, IBS constipation, reflux, dysmotility, and pain. The number of items had been reduced to

34 after evaluation in 690 primary care patients with heartburn or abdominal pain. The Functional Digestive Disorder Quality of Life questionnaire (FDDQOL) was also developed by item reduction.(31) The scale was designed for use in dyspeptic and IBS patients. It includes 43 items with eight different domains. Its psychometric validity was tested in a multinational randomised controlled trial involving 401 patients with functional gastrointestinal disorders.(31) The final QOL instrument we evaluated was the Irritable Bowel Syndrome Health Related Quality of Life questionnaire (IBS-HRQOL), developed by Wong et al.(32) This measure was developed by item reduction and factor analysis involving data from 100 IBS patients. It includes 26 items on bowel symptoms, fatigue, limitation of activities and emotional dysfunction.

Validity assessment of symptom scales

The "Adequate Relief" question scored best on all 12 assessment criteria (Table 2). This measure has been sufficiently validated, is easy to administer, and is appropriate for use. The reviewers agreed that the scale showed responsiveness, and face-, content- and construct validity. Its internal consistency, however, was considered poor and its content validity debatable. In the psychometric evaluation, the AR showed a significant correlation with improvement in pain severity scores, percentage of pain-free days, days with urgency, improvement in stool frequency, -consistency, and quality of life parameters (SF36 and IBS-QOL).(16) One reviewer had doubts about the clinical relevance of the score, because the AR only includes scores on abdominal pain or discomfort. The IBS-SSS showed both good psychometric and methodological qualities and in the reviewers' judgement, is appropriate for use. Its practical utility, however, was considered debatable, and its reliability has yet not been assessed because the measure has not been tested in other populations. The GSRS showed appropriate validity. However, the reviewers found its clinical relevance difficult to establish, because the instrument consists of five subscales that are not specific for IBS. Like the GSRS, the FBDSI does not score IBS specific symptoms. Moreover, its specific responsiveness in IBS could not be judged. The FBDSI has, however been validated in IBS patients, the validation population has been adequately described, and the instrument is easy to administer and appropriate for use. The IBS-Q showed internal consistency, but insufficient quality with regard to the other psychometric and methodological criteria. Moreover, the validation population was insufficiently described and the validation report did not provide information on the responsiveness for all included IBS symptoms (Rome criteria). The instrument also showed weak correlations with the global ratings of patients' IBS symptoms and average daily pain scores.

None of the validity evaluations of the symptom-based questionnaires included primary care IBS patients with and none had been used in a primary care setting.

Table 2. Comparison of psychometric and methodological properties of standardized IBS outcome measures: symptom questionnaires

Instrument	Assessment criteria (see table 1)											
	A	B	C	D	E	F	G	H	I	J	K	L
AR	-	+	+	±	+	+	+	+	+	+	+	-
IBS-SSS	-	+	+	+	+	+	±	+	+	±	+	-
GSRS	+	±	+	+	+	±	±	+	±	-	-	-
FBDSI	-	-	±	+	+	±	+	+	+	±	+	-
IBS-Q	+	+	±	±	±	-	-	±	±	+	±	-

+: five or more reviewers agree that the measure satisfies the assessment criterion.
±: five or more reviewers agree that the measure partly satisfies the criterion or less than five agree that it fully meets the criterion, or less than five agree that it does not meet the criterion.
-: five or more reviewers agree that the measure does not satisfy the assessment criterion or that the measure provides no information on the assessment criterion.
AR, adequate relief of abdominal pain/discomfort; IBS-SSS, IBS symptom severity score; GSRS-IBS, gastrointestinal symptom rating scale IBS; FBDSI, functional bowel disorder severity index; IBS-Q, IBS symptom questionnaire.

Validity assessment of QOL instruments

The IBS-QOL was the most extensively validated of all the QOL measures and showed both accurate psychometric and methodological qualities (Table 3). The reviewers agreed that this scale is valid, responsive, and reliable in referred IBS patients. The IBSQOL on the other hand was only reasonably validated; it lacked responsiveness and is difficult to interpret. Moreover, with regard to psychometric evaluation, the IBSQOL had been tested in only one clinical trial. All reviewers agreed that the population in that trial was not fully described, since the inclusion criteria were not clearly defined. One reviewer also had doubts about the quality of the validation process. The DHSI showed moderate validity. Its appropriateness for use was difficult to assess because the validation paper did not include the questionnaire, and the validation population was not properly described. Furthermore, it was, however, the only instrument tested in a primary care setting. The FDDQOL had sufficient psychometric quality, but unsatisfactory methodological quality. In addition, all of the reviewers agreed that its practical utility was debatable. The IBS-HRQOL has not yet been satisfactorily validated.

The interpretability of most of the QOL instruments is considered questionable since they had not been compared with a clinically relevant outcome or showed poor correlations. The IBSQOL was difficult to interpret, because it lacks a clear correlation with other clinically relevant outcome parameters. With regard to the psychometric evaluation, the IBS-QOL showed strong correlations with the SF36 subscales bodily pain and social functioning and with the FBDSI's moderate to severe IBS.(28)
The practical utility of all five HRQOL instruments in daily practice was considered debatable. All of the reviewers found these measures lengthy and cumbersome in use.

Table 3.Comparison of psychometric and methodological properties of standardised IBS outcome measures: quality of life questionnaires

Instrument	Assessment criteria (see table 1)											
	A	B	C	D	E	F	G	H	I	J	K	L
IBS-QOL	+	+	+	+	±	±	±	+	+	+	+	-
IBSQOL	±	-	+	+	+	-	±	+	±	±	±	-
DHSI	+	-	+	±	±	±	±	±	±	±	+	+
FDDQOL	+	±	+	+	±	±	±	±	±	±	±	-
IBS-HRQOL	-	-	±	±	-	±	±	±	+	±	±	-

+: five or more reviewers agree that the measure satisfies the assessment criterion.
±: five or more reviewers agree that the measure partly satisfies the criterion or less than five agree that it fully meets the criterion, or less than five agree that it does not meet the criterion.
-: five or more reviewers agree that the measure does not satisfy the assessment criterion or that the measure provides no information on the assessment criterion.
IBS-QOL, IBS quality of life measurement; IBSQOL, IBS quality of life questionnaire; DHSI, digestive health status instrument; FDDQOL, functional digestive disorder quality of life questionnaire; IBS-HRQOL, irritable bowel syndrome health-related quality of life questionnaire.

Discussion

We identified 10 standardised questionnaires for outcome assessment in IBS research: 5 symptom scores and 5 IBS-specific QOL instruments. Some showed reasonable psychometric and methodological qualities, but most missed at least one quality item. Based on our results the patient-defined "Adequate Relief of abdominal pain and discomfort" is currently the best choice for the assessment of global symptomatology. In order to obtain more information on more specific symptoms, an integrated symptom scale may be used as a secondary outcome measure.

According to our criteria, the IBS-SSS is, the best instrument to obtain this information. The IBS-QOL is preferred to establish changes in health-related quality of life

Although readily available, not one of the symptom scales is optimal. The outcome of the Adequate Relief measure, for example is scored on a dichotomous scale. Although these scales are easy to apply, their use has been criticised since they decrease the sensitivity (power) in detecting clinically relevant changes.(4) Visual analogue scales (VAS), like that used in the IBS-SSS, can also be criticised since many patients report difficulties using them.(4) With regard to the GSRS, symptom assessment can only be performed if a lower methodological quality is acceptable. Finally, neither the FBDSI nor the IBS-Q can be recommended as the optimal outcome measure in IBS treatment trials. The FBDSI was for example originally developed for functional gastrointestinal disorders, but the severity score does not include IBS symptoms, moreover its responsiveness is difficult to determine. The IBS-Q requires further validation in order to evaluate its responsiveness and reliability.

All of the IBS-specific HRQOL instruments we identified must also be considered suboptimal outcome measures since they are not practical to use and most lack responsiveness. Our views on psychometric and methodological quality are in line with the conclusions of a recent review on HRQOL outcomes.(13)

The methodology we used provides a detailed scientific basis for outcome research in IBS since we included both psychometric and methodological assessment criteria. Nevertheless, it also has limitations. For example, we expect that the participation of reviewers from different countries and backgrounds will limit the subjective interpretation. Further, there are no strict guidelines regarding the definition of consensus in outcome research. In fact, a recent review on consensus development methods concluded that consensus should be based on the user' own common sense and on that of previous users.(33) For the present study, we defined consensus as agreement between five of the six reviewers in the same category score so that more than 80% agreement was reached on every single assessment criterion.

Most of the IBS scales we considered have not yet been sufficiently evaluated in drug trials, and only one was validated in primary care setting. In fact, all but the DHSI were developed and evaluated at the secondary care level. This seems contradictory since IBS is the most commonly seen gastrointestinal disorder at the primary care level and only a minority of these patients is referred to secondary care.(34) Because of this and the fact that primary care patients may respond differently to therapy, further evaluation of these outcome measures should be conducted in the clinical trials at the primary care level.

References

1. Drossman DA. Irritable bowel syndrome: diagnosis, subgrouping, management, and clinical trial design. Proceedings of a symposium. Am J Med 1999;107 (5A)
2. Veldhuyzen van Zanten SJO, Tally NJ, Bytzer P, et al. Design of treatment trials for functional gastrointestinal disorders. Gut 1999;45 (SupplI):69-77.
3. Whitehead WE, Corazziari E, Prizont R, et al. Definition of a responder in clinical trials for functional gastrointestinal diseases: report on a symposium. Gut 1999;45 (Suppl II):78-9.
4. Naliboff B, Fullerton S, Mayer EA. Measurement of symptoms in irritable bowel syndrome clinical trials. Am J Med 1999;107:81S-4S.
5. Bergner M, Bobbitt RA, Carter WB, et al. The sickness impact profile: Development and final revision of a health status measure. Med Care 1981;19:787-805.
6. Revicki DA, Leidy NK, Howland L. Evaluating the psychometric characteristics of the Psychological General Well-Being index with a new response scale. Qual Life Res 1996;5:419-24.
7. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36) I. Conceptual framework and item selection. Med Care 1992;30:473-83.
8. Whitehead WE, Burnett CK, Cook EW, et al. Impact of irritable bowel syndrome on quality of life. Dig Dis Sci 1996;41:2248-53.
9. Bergman JF, Chassany O. The role of quality of life in functional gastrointestinal disorders: regulatory issues. Eur J Surg 1998;Suppl 583:87-91.
10. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med 1993;118:622-9.
11. Talley NJ, and the working team for design of treatment trials. In: Drossman DA, ed. The functional gastrointestinal disorders: diagnosis, pathofysiology and treatment. McLean, VA: Degnon Associates; 1994; 7, Optimal design of treatment trials. p. 265-310.
12. Fitzpatrick R, Fletcher A, Gore S, et al. Quality of life measures in health care I: Applications and issues in assessment. BMJ 1992;305:1074-7.
13. Borgankar L, Irvine EJ. Quality of life measurement in gastrointestinal and liver disorders. Gut 2000;47:444-54.
14. Fitzpatrick R, Fletcher A, Gore S, et al. Quality of life measures in health care. II: Design, analysis, and interpretation. BMJ 1992;305:1145-8.
15. Mangel AW, Hahn B, Heath AT, et al. Adequate relief as an endpoint in clinical trials in irritable bowel syndrome. J Int Med Res 1998;26:76-81.(int/intern?)

16. Camilleri M, Northcutt AR, Kong S, et al. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. Lancet 2000;355:1035-40.
17. Wiklund I, Fullerton S, Hawkey CJ et al. A patient-based symptom questionnaire for use in irritable bowel syndrome. Poster presentation. DDW 2000. San Diego, CA, USA 2000.
18. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997;11:395-402.
19. Revicki DA, Wood M, Wiklund I, et al. Reliability and validity of the gastrointestinal symptom rating scale in patients with gastroesophageal reflux disease. Qual Life Res 1998;7:75-83.
20. Svedlund J, Sjoedin I, Dotevall G. GSRS - a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988;33:129-34.
21. Drossman DA, Zhiming LI, Toner BB, et al. Functional Bowel Disorders. a multicenter comparison of health status and development of illness severity index. Dig Dis Sci 1995;40:986-95.
22. Drossman DA, Whitehead WE, Toner BB, et al. What determines severity among patients with painful functional bowel disorders. Am J Gastroenterol 2000;95:974-80.
23. Sperber AD, Carmel S, Atzmon Y, et al. Use of the functional bowel disorder severity index (FBDSI) in a study of patients with the irritable bowel syndrome and fibromyalgia. Am J Gastroenterol 2000;95:995-8.
24. Goka AK, Sandy JW. Development and validation of an IBS symptom questionnaire and the relevance of the Rome Criteria to selection of patients for IBS clinical trials. Proceedings MWT symposium 'Definition of a responder in clinical trials for functional bowel disorders'. Vienna. Sept. 10-11, 1998.
25. Patrick DL, Drossman DA, Frederick IO, et al. Quality of life in persons with irritable bowel syndrome. Development and validation of a new measure. Dig Dis Sci 1998;43:400-11.
26. Drossman DA, Patrick DL, Whitehead WE, et al. Further validation of the IBS-QOL: a disease-specific quality-of-life questionnaire. Am J Gastroenterol 2000;95:999-1007.
27. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. Digestion 1999;60:77-81.

28. Hahn BA, Kirchdoerfer LJ, Fullerton S, et al. Evaluation of a new quality of life questionnaire for patients with irritable bowel syndrome. Aliment Pharmacol Ther 1997;11:547-52.
29. Hahn BA, Kirchdoerfer LJ, Fullerton S, et al. Patient-perceived severity of irritable bowel syndrome in relation to symptoms, health resource utilization and quality of life. Aliment Pharmacol Ther 1997;11:553-9.
30. Shaw M, Talley N J, Adlis S, et al. Development of a digestive health status instrument: test of scaling assumptions, structure and reliability in a primary care population. Aliment Pharmacol Ther 1998;12:1067-78.
31. Chassany O, Marquis P, Scherrer B, et al. Validation of a specific quality of life questionnaire for functional digestive disorders. Gut 1999;44:527-33.
32. Wong E, Guyatt GH, Cook DJ, et al. Development of a questionnaire to measure quality of life in patients with irritable bowel syndrome. Eur J Surg Suppl 1998;253:50-6.
33. Black N, McMurphy M, Lamping D, et al. Consensus development methods: a review of best practice in creating clinical guidelines. J Health Serv Res Policy 1999;4:236-48.
34. Janssen HAM, Borghouts JAJ, Muris JMW, et al. Health status and management of chronic non-specific abdominal complaints in general practice. Br J Gen Pract 2000;50:375-9.

Chapter 6

Randomised patients in irritable bowel syndrome research had different disease characteristics compared to eligible and recruited patients

Bijkerk CJ, Muris JWM, Knottnerus JA, Hoes AW, de Wit NJ. Randomised patients in IBS research had different disease characteristics compared to eligible and recruited patients. *Clin J Epidemiol.* Accepted for publication.

Abstract

Objective: The recruitment process may generate a selected patient sample, which may threaten the generalisability of trial results. This risk is particularly high in case disease and patient characteristics demonstrate a wide variation, such as in irritable bowel syndrome (IBS). We compared IBS patients who were selected, approached and randomised to participate in a clinical trial assessing the efficacy of dietary fibre therapy in IBS.

Study design and setting: Retrospective survey in primary care patients diagnosed with IBS by their GP in the past two years selected and invited for participation in a trial. Characteristics were compared between randomised patients (RP, n=193) non-randomised eligible patients (NREP, n=371) and patients not eligible for participating in the trial (NEP, n=724).

Results: Of the 2100 IBS patients, 1288 (61%) returned the questionnaire. Randomised patients had a higher intensity of IBS abdominal pain as compared to the other groups, a higher consultation rate and a longer IBS disease history. Non eligible patients had less active IBS symptoms.

Conclusion: Patients randomised do differ from those non-randomised in IBS disease characteristics. These observations may have implications for the applicability of our research outcome.

Introduction

Irritable bowel syndrome (IBS) is the most common functional gastro-intestinal disorder in clinical practice and an important focus for clinical research.(1) The study population in IBS research is often a highly selected sample of the clinically relevant patient group. If the inclusion process is a modifier of the trial outcome, that is, if the treatment effect in not included subjects would be different, this results in a lack of generalisability of the trial results to the population in which the study results should be applied.(2-4)

The generalisability of research results is particularly threatened in medically unexplained diseases such as chronic fatigue, syndrome, whiplash, fibromyalgia and irritable bowel syndrome. These functional somatic syndromes share a number of typical features.(5) They are poorly defined, usually by expert based diagnostic criteria. Patients generally have high consultation rates, a long standing disease history and experience a serious impact on quality of life. Patients have an increased prevalence of somatic and psychiatric comorbidity and a higher burden of major life events. The placebo effect is high, varying from 30 to 60%, the effectiveness of drug therapy is generally limited and patients are often sensitive to central nervous system modulating interventions.

The prevalence of these typical disease characteristics is affected by consultation and referral.(6;7) Consulting IBS patients do have a different psychological profile compared to those who do not consult.(8) Referred IBS patients have more pain, and more frequent complaints as compared those in primary care.(9-12). Most functional disease research is conducted in patients in secondary and tertiary care setting. Drug trials include only patients fulfilling the strict diagnostic criteria (e.g. the Rome diagnostic criteria for IBS) which lack validity in the primary care setting.(13;14) The applicability of research results in the clinical setting may often be questioned, especially in functional disease research and requires a strict monitoring of the inclusion and selection process of the patient sample.

We recently conducted a randomised controlled trial (RCT) comparing the efficacy of psyllium (soluble fibre), bran (insoluble fibre), and placebo in primary care patients with irritable bowel syndrome. We studied the recruitment and inclusion process of the trial in detail and report differences in demographic and clinical characteristics between randomised and eligible but non randomised patients that may limit the generalisability of the trial results.

Study design and setting

Patients were recruited from 43 primary care practices located in the central and southern areas of the Netherlands. Six practices were part of the University primary care network in Utrecht and Maastricht, the other practices collaborated on ad hoc basis. Patients in both networks are representative for the Dutch population.(15) The practices comprise about 200,000 patients served by 99 general practitioners (GPs). The participating GPs were asked to select patients aged 18-65 years and who were diagnosed with and consulted for IBS in the past two years. Patients were identified through their electronic medical files (EMF) using the ICPC code D93 (IBS) and the free texts words 'IBS'. Patients were sent an invitation to participate in a placebo controlled RCT studying the efficacy of psyllium or bran in relieving IBS symptoms. Patients with 'definite' IBS (according to the Rome II diagnostic criteria for IBS) (figure 1) as well as those with 'probable' IBS (pragmatically diagnosed with IBS by their GP) with active IBS symptoms in the past 4 weeks were eligible for inclusion. Patients with alarm symptoms, those on active fibre treatment, under specialist treatment for IBS, using anti-depressive medication, and those unable to fill out the questionnaires were excluded (usually because they did not master the Dutch language). After giving informed consent eligible patients were randomly allocated to three groups, receiving either 10 gram psyllium (soluble fibre), 10 gram bran (insoluble fibre), or 10 gram rice wheat (placebo) per day during 12 weeks. The primary outcome was adequate relief of abdominal pain or discomfort.

Figure 1. Rome II diagnostic criteria for IBS

At least 12 or more consecutive weeks in the preceding 12 months, of abdominal discomfort or pain with at least two of the three following features:

1. Relieved with defecation; and/or
2. Onset associated with a change in stool frequency; and/or
3. Onset associated with change in stool consistency

Symptoms that further support the diagnosis of irritable bowel syndrome:

- Abnormal stool frequency (more than 3 bowel movements per day and less than 3 bowel movements per week)
- Abnormal stool form (lumpy/hard or loose/watery stool)Abnormal stool passage (straining, urgency, or feeling of incomplete evacuation)
- Passage of mucus
- Bloating or feeling of abdominal distension

In absence of structural or metabolic abnormalities to explain the symptoms

Questionnaire

All patients that were approached for participation received an invitational letter together with an IBS symptom checklist. We assessed the severity of IBS-related symptoms using a visual analogue scale (VAS) (0% to 100%) of the IBS symptom severity scale (IBS-SSS), a questionnaire that includes the Rome II diagnostic criteria for IBS and was designed to measure the treatment response of symptoms and well-being in patients suffering from IBS.(16) The IBS-SSS is, the best instrument to obtain differences between-patient in IBS symptoms.(17) A VAS score is valid and reliable of measuring severity of pain.(18) We added questions about the duration of IBS, additional gastro intestinal symptoms, the use of medication for depression or anxiety, and details of specialist referral. Patients not responding to the invitation received a postal reminder. Even when they were not willing to participate in the RCT, they were explicitly asked to return the completed questionnaire.

Patients

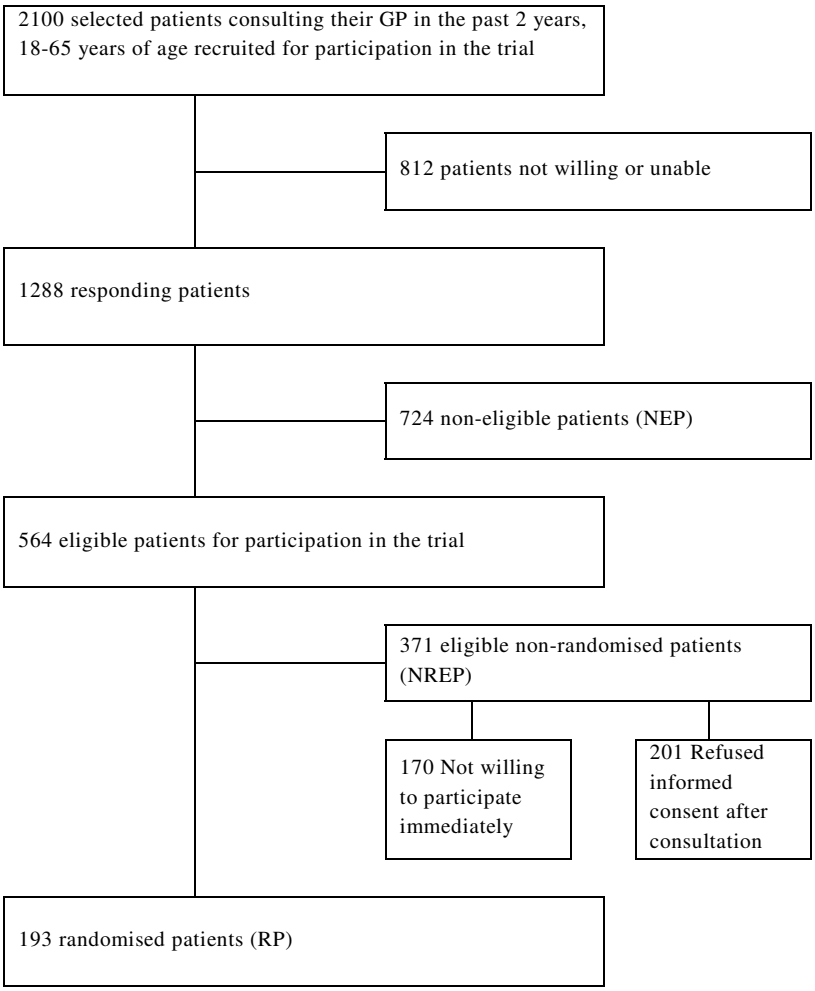
Through the EMF of the participating practices 2100 IBS patients were pre-selected and approached for participation. The response rate was 61% (n=1288). Responders and non responders did not differ with respect to age and gender. After selection a total of 564 patients (44%) were eligible for participation (ENRP), 34% of these patients were randomised (n=193). According to figure 2, 126 patients were not willing to participate immediately and 245 refused informed consent after consultation. For various reasons (second thoughts, non eligibility or no time) these patients refused further participation. The randomised patients (RP) formed 15% of the respondents, and 34% of the eligible responders (figure 2). Of the eligible patients 66% did not consent to randomisation (ENRP, n=371). More than half of them declined participation after consulting their GP, the rest decided not to participate after reading the postal invitation. The remaining 724 patients (57% of the responders) were non eligible patients (NEP). In summary, 61% of the patient with the disease under study in participating centres showed interest in our study, 27% was eligible for participation and finally 9% was randomised. Major reasons for non eligibility were: no active IBS symptoms in the past four weeks (78%), having received a fibre prescription in the past 4 weeks (10%), active treatment for anxiety and depression (12%), and treatment for IBS in secondary care (14%).

Analysis

We compared the demographic, clinical and the disease-specific characteristics of the randomised patients (RP) with those of the eligible but non-randomised patients

(ENRP) and the non eligible IBS patients (NEP). Relations between categorical data and variables that were analysed with univariate ANOVA and independent student t-tests for mean scores and $\chi 2$ tests for categorical variables. We used SPSS for windows 12.0.1 (SPSS, Inc. Chicago, Illinois, USA) for statistical procedures.

Figure 2. Flowchart of 2100 IBS patients identified and recruited for trial participation



Results

Table 1 shows the demographic and disease-specific characteristics of the 3 subgroups of responding IBS patients. The 3 patient groups did not differ in the male/female ratio and mean age.

Table 1. Demographic and disease-specific characteristics

	Randomised patients (n = 193)		Eligible non randomised patients (n = 371)		Non eligible patients (n=724)		P
Characteristic	n	% Mean	n	% Mean	n	% Mean	
Gender							
Male	38	19.7	83	22.7	173	26.1	0.15
Female	155	80.3	283	77.3	491	73.9	
Mean Age (years)	193	41.4	371	38.2	724	41.7	0.16
Consulted GP for IBS							
Last month	26	14.4	39	10.5	54	7.5	<0.001
Last 3-6 months	76	40.0	120	32.3	175	26.1	
Last 1year	54	27.2	105	28.3	241	33.3	
More than 1 year ago	37	18.3	107	28.8	254	35.1	
History of abdominal symptoms	48	24.9	115	30.9	196	27.1	<0.001
0-2 years	55	28.7	90	24.3	300	41.4	
2-5 years	34	18.2	67	18.1	92	12.7	
5-10 years	56	28.2	99	26.5	136	18.8	
>10 years							
IBS related symptoms							
Abdominal pain	151	79.4	371	100	134	21.7	<0.001
Diarrhoea	73	41.6	150	40.4	132	18.2	<0.001
Constipation	65	35.7	144	38.8	159	22.0	<0.001
Loose stools	70	39.3	140	37.7	108	14.9	<0.001
Hard stools	104	58.6	232	62.5	233	32.2	<0.001
Straining	94	52.0	210	56.6	215	29.7	<0.001
Urgency	96	53.2	179	48.2	186	25.7	<0.001
Incomplete evacuation	121	66.9	234	63.1	247	34.3	<0.001
Mucus	71	38.7	99	26.7	102	14.1	<0.001
Bloating	172	91.1	333	89.8	413	57.0	<0.001
Mean IBS symptom severity (VAS 0-100)	193	41.1	371	34.4	724	18.6	<0.001
IBS symptom severity							
Mild (<24)	32	14.9	87	23.5	416	57.5	<0.001
Moderate (25-74)	142	75.1	271	73.0	282	39.0	<0.001
Severe (>=75)	19	9.9	13	3.5	26	3.9	<0.001
IBS according to Rome II criteria	70	36.3	114	30.7	92	12.7	<0.001
IBS subtype							
IBS Constipation	122	63.2	274	73.9	306	42.3	<0.001
IBS Diarrhoea	52	26.9	76	20.5	132	18.2	0.27

In line with the inclusion criteria for all patients the diagnosis of IBS was confirmed during primary care consultation in the past 2 years. The randomised patients had consulted their GP more frequently in the past year than the eligible non randomised patients and the non eligible patient group. A larger proportion of randomised patients had an IBS disease history longer than 10 years (28.2%) as compared to eligible non randomised patients (18.8%). The group of randomised patients had more frequently abdominal pain and significant differences were found with respect to IBS symptom intensity (measured by VAS). Randomised patients had a higher pain intensity; the mean VAS-score of the patients in the randomised group was 41.1 (SD 21.4), compared to 34.4 (SD 20.2) in the eligible non randomised patients and 18.6 (SD 22.1) in the non eligible patients. Randomised patients had also more severe IBS abdominal pain, as categorised according to the VAS score. The prevalence of IBS-related symptoms such as bloating, hard stools, incomplete evacuation of mucus varied significantly between the different groups. The proportions of patients with hard stools and mucus in the stool were more prevalent amongst the eligible non randomised patients. A larger proportion of the randomised patients had IBS symptomatology which fulfilled the Rome II criteria (81.1%) as compared to the non eligible patients (12.7%). The distribution of the subgroup of IBS patients with constipation was significantly different amongst the groups. IBS predominant constipation was more prevalent among the RP (63.2%) and eligible non randomised patients (73.9%) as compared to the non eligible patients (42.3%). Patients not willing to participate more frequently consulted their GP in the past months as compared to patients who refused informed consent after consultation, but did not differ with respect to gender, age, history, subtype of IBS and symptom severity.

Discussion

To our knowledge this is the first IBS study in which the recruitment process was monitored in detail, facilitating conclusions regarding the generalisability of the trial results. Successful implementation of trial results in clinical practice depends on their applicability. The key condition for representiveness of the trial population in clinical research is that the inclusion process creates a study population that does not differ significantly from the patient population in daily clinical care. We have demonstrated that in our trial randomised IBS patients had more IBS symptoms and more severe abdominal pain, a longer IBS history, more frequent consultations and different subtypes of IBS as compared to IBS patients who refused or were not eligible for participation. These differences may have influenced the outcome of the intervention under study. Patients with more abdominal pain or those with a longer

history of IBS may have higher expectations from fibre treatment than those who did not give informed consent. Moreover patients with a long standing functional disease history are reported to have more somatic and psychiatric comorbidity and may therefore be more resistant to therapy.(19) Some of the non eligible IBS patients were excluded because they had already used fibre therapy, possibly with negative results. If fibre therapy achieves its effectiveness primarily through improving stool consistency the randomised group (with more constipation predominant IBS) was more likely to benefit.

Limitations

For the nonrandomised patients information on some potential effect modifiers, such as socioeconomic status, quality of life, number of visits and comorbidity, was not available. Therefore for these determinants comparisons with the randomised patients was not possible. As was previously suggested by van den Akker et al (20) it seems likely that differences in comorbidity patterns may have further contributed to the selection process.

Implications

In the critical assessment of clinical trials clinicians should consider the characteristics of the study population and compare them with the patient group they encounter in daily clinical care. Feinstein specified "interiatric referral" as an important factor affecting "the likelihood that patients will appear at the particular setting in which research is being conducted".(3)

We have shown that in our RCT on dietary fibre treatment IBS patients who were randomised differed from the eligible IBS patient population in primary care, especially with respect to symptomatology and disease history, which may modify the treatment effect. These observations may have implications for the applicability of our results, in case subgroup analysis confirms that the effectiveness of fibre therapy depends on IBS symptom severity.

Non selective recruitment of patients for clinical trials is probably non realistic. Although commonly applied, prospective monitoring of all eligible patients, also those non-randomised, proves difficult to achieve in daily practice. Time constraints may lead to incomplete recording of non-randomised but eligible patients. We used retrospective selection of potential participants in the electronic medical file, and found it was a useful and feasible alternative recruitment procedure. However, as we demonstrated in this study it does not overcome the problem of selection bias as a result of the recruitment process.(20)

References

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006 Apr;130(5):1480-91.
2. Jones R. Likely impacts of recruitment site and methodology on characteristics of enrolled patient population: irritable bowel syndrome clinical trial design. Am J Med 1999 Nov 8;107(5A):85S-90S.
3. Knottnerus JA. Between iatrotropic stimulus and interiatric referral: the domain of primary care research. J Clin Epidemiol 2002 Dec;55(12):1201-6.
4. Knottnerus JA. Medical decision making by general practitioners and specialists. Fam Pract 1991 Dec;8(4):305-7.
5. Henningsen P, Zipfel S, Herzog W. Management of functional somatic syndromes. Lancet 2007 Mar 17;369(9565):946-55.
6. Talley NJ, Boyce PM, Jones M. Predictors of health care seeking for irritable bowel syndrome: a population based study. Gut 1997 Sep;41(3):394-8.
7. Drossman DA, McKee DC, Sandler RS, Mitchell CM, Cramer EM, Lowman BC, et al. Psychosocial factors in the irritable bowel syndrome. A multivariate study of patients and nonpatients with irritable bowel syndrome. Gastroenterology 1988 Sep;95(3):701-8.
8. Koloski NA, Talley NJ, Boyce PM. Predictors of health care seeking for irritable bowel syndrome and nonulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors. Am J Gastroenterol 2001 May;96(5):1340-9.
9. Longstreth GF, Hawkey CJ, Mayer EA, Jones RH, Naesdal J, Wilson IK, et al. Characteristics of patients with irritable bowel syndrome recruited from three sources: implications for clinical trials. Aliment Pharmacol Ther 2001 Jul;15(7):959-64.
10. Bijkerk CJ, de Wit NJ, Stalman WA, Knottnerus JA, Hoes AW, Muris JW. Irritable bowel syndrome in primary care: the patients' and doctors' views on symptoms, etiology and management. Can J Gastroenterol 2003 Jun;17(6):363-8.
11. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. Gut 2000 Jan;46(1):78-82.
12. Van der Horst HE, van Dulmen AM, Schellevis FG, van Eijk JT, Fennis JF, Bleijenberg G. Do patients with irritable bowel syndrome in primary care really differ from outpatients with irritable bowel syndrome? Gut 1997 Nov;41(5):669-74.

13. Vandvik PO, Aabakken L, Farup PG. Diagnosing irritable bowel syndrome: poor agreement between general practitioners and the Rome II criteria. Scand J Gastroenterol 2004 May;39(5):448-53.
14. Mearin F, Badia X, Balboa A, Baro E, Caldwell E, Cucala M, et al. Irritable bowel syndrome prevalence varies enormously depending on the employed diagnostic criteria: comparison of Rome II versus previous criteria in a general population. Scand J Gastroenterol 2001 Nov;36(11):1155-61.
15. Hak E, Rovers MM, Kuyvenhoven MM, Schellevis FG, Verheij TJ. Incidence of GP-diagnosed respiratory tract infections according to age, gender and high-risk comorbidity: the Second Dutch National Survey of General Practice. Fam Pract 2006 Jun;23(3):291-4.
16. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997 Apr;11(2):395-402.
17. Bijkerk CJ, de Wit NJ, Muris JW, Jones RH, Knottnerus JA, Hoes AW. Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics. Am J Gastroenterol 2003 Jan;98(1):122-7.
18. Naliboff BD, Fullerton S, Mayer EA. Measurement of symptoms in irritable bowel syndrome clinical trials. Am J Med 1999 Nov 8;107(5A):81S-4S.
19. Guthrie EA, Creed FH, Whorwell PJ, Tomenson B. Outpatients with irritable bowel syndrome: a comparison of first time and chronic attenders. Gut 1992 Mar;33(3):361-3.
20. de Wit NJ, Quartero AO, Zuithoff AP, Numans ME. Participation and successful patient recruitment in primary care. J Fam Pract 2001 Nov;50(11):976.

Chapter 7

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

Published as: Bijkerk CJ, Muris JWM, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different type of fibres in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther.* 2004;19:245-251.

Abstract

Objectives: 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 (IBS). IBS patients with constipation might have a delayed intestinal transit. Therefore fibres that accelerate intestinal transit may be beneficial for these patients. The uncertain benefits reported by several clinical studies, however, led us to reappraise the value of fibre in IBS management. This study was performed to quantify the effect of different types of fibre on global and symptom relief from IBS.

Methods: Using a structured literature search in MEDLINE (1966-2002), we selected randomised controlled trials involving IBS patients treated with fibres. Analyses were done for the total group and for trials using soluble and insoluble fibres separately.

Results: Seventeen studies were included in the analysis. None of them investigated primary care IBS patients. Fibre in general, is effective in the relief of global IBS symptoms (RR 1.33 (95% CI: 1.19-1.50)). IBS patients with constipation might have benefit from fibre treatment (RR 1.56 (95CI: 1.21-2.02)), while there is no evidence that fibre is effective in the relief of abdominal pain in IBS. Soluble fibre (psyllium, ispaghula, calcium polycarbophil) showed significant improvement (RR 1.55 (95%CI: 1.35-1.78)), while insoluble fibre (corn, wheat bran) might in some IBS patients worsen the clinical outcome, but there was no significant difference compared to placebo (RR 0.89 (95%CI: 0.72-1.11)).

Conclusions: The benefits of fibre in the treatment of IBS are marginal for global IBS symptom improvement and IBS-related constipation. Soluble and insoluble fibres have a different effect on global IBS symptoms. Insoluble fibres might, in fact, in some patients worsen the clinical outcome. Future clinical studies, evaluating the effect and tolerability of fibre therapy, are needed in primary care.

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by recurrent episodes of abdominal pain/discomfort and disturbed bowel habits.(1) It is very common, in both primary and secondary care.(2-4) The aetiology of IBS 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) IBS patients consulting their primary care doctor often receive dietary advice, are 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 IBS.(4,5) In fact, advice to increase the fibre content of their diet is given to 20-36% of all primary care IBS 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 gut transit time. This shortened transit time may alleviate constipation and decrease intra-colonic 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 IBS patients.(9,10,11) Others have suggested that bran, in fact, may worsen IBS symptoms.(12,13)

Systematic reviews have shown that treatment of IBS patients with fibres remains controversial.(14-18) Some have either reported on global IBS symptoms or IBS related symptoms, but none of these analysed the results for soluble and insoluble fibres separately. In the present meta-analysis, therefore, the aim was to quantify the effectiveness of different types of fibre measured by varied 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 (MeSH) terms "functional colonic diseases", "dietary fibre", and "randomised 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 randomised-controlled trials with a randomised or quasi-randomised allocation of intervention were considered eligible for analysis. We concentrated on the following outcome measures: the proportion of patients reporting clinical relief (global IBS symptom improvement); the proportion of patients who had improved IBS-related abdominal pain; and the proportion of patients who reported improvement in IBS-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 using fixed-effects models. Heterogeneity between studies was explored using chi-square tests. If the effect size estimates varied to a greater extend than on the basis of chance alone, a random-effect model was used. Improvement of IBS symptoms using fibre treatment was considered significantly better than control when the lower limit of the 95% confidence interval was >1. Fibre treatment significantly worsened IBS symptoms when the upper limit of the 95% confidence was <1. Analyses were done for the total group and for trials using soluble and insoluble fibres separately.

Results

Trials identified

Of the 35 studies found, 20 were considered 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 seventeen studies for the meta-analysis, involving a total of 1363 IBS 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 IBS patients. Table 1 summarizes the specifications of all included studies.

Efficacy of fibres

Twelve trials reported on global IBS symptom improvement. The pooled relative risk (RR) was 1.33 (95%CI: 1.19-1.50) (Figure 1). Fibre treatment was successful in more than half (60%) of the IBS patients. There is no evidence that fibre is effective in IBS patients with abdominal pain (Figure 2). In fact, fibre might, in some IBS patients worsen the clinical outcome (RR 0.78 (95%CI: 0.64-0.95)). The pooled effect of fibre treatment on IBS-related constipation, was more favourable than placebo (RR 1.56 (95%CI: 1.21-2.02)) (Figure 3).

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

Study	Year of publication	Treatment	Dose (per day)	Study design	Duration (weeks)	Outcome measure
Soluble fibre						
Arthurs (23)	1983	Ispaghula	2 sachet	DB	4	Global IBS symptoms
Golecha (24)	1982	Ispaghula	NA	DB	3	Abdominal pain
Jalihal (25)	1999	Ispaghula	30g	DB	4	Global IBS symptoms, abdominal pain, constipation
Longstreth (26)	1981	Psyllium	6.4g	DB	8	Global IBS symptoms, abdominal pain, constipation
Nigam (27)	1984	Ispaghula	NA	DB	NA	Global IBS symptoms
Prior (28)	1987	Ispaghula	1 sachet*	DB	12	Global IBS symptoms, abdominal pain, constipation
Ritchie1 (30)	1979	Ispaghula	1 sachet*	DB	12	Global IBS symptoms
Ritchie2 (31)	1980	Ispaghula	1 sachet*	DB	12	Global IBS symptoms
Toskes (29)	1993	Calcium polycarbophil	6g	DB	12	Global IBS symptoms

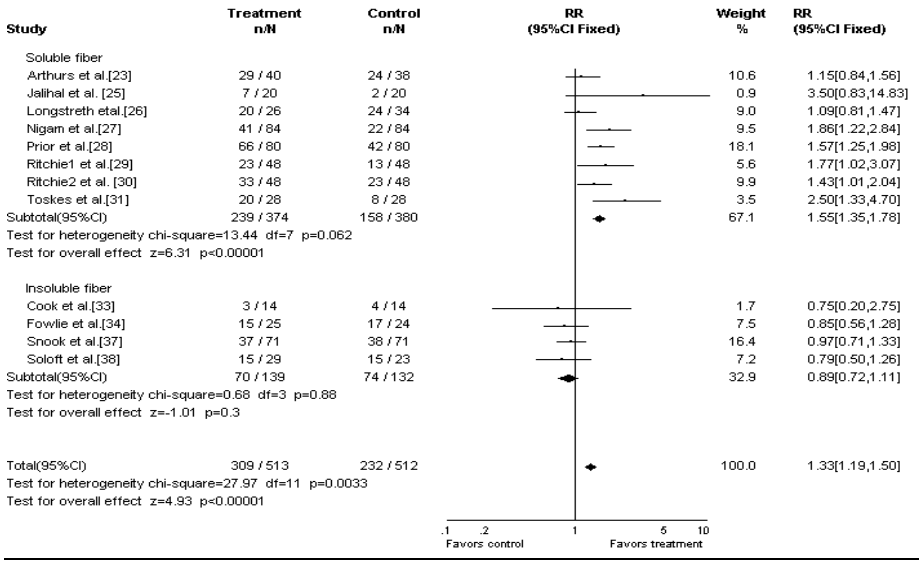
DB: double-blinded trial; SB: single-blinded trial; O: open trial NA not applicable, 1 sachet is approximately 5 gram.

Table 1. Continued

Study	Year of publication	Treatment	Dose (per day)	Study design	Duration (weeks)	Outcome measure
Insoluble fibre						
Cann (32)	1984	Wheat bran	10-30g	DB	9	Abdominal pain, constipation
Cook (33)	1990	Corn fibre	20g	DB	12	Global IBS symptoms
Fowlie (34)	1992	Wheat bran	4.1g	DB	12	Global IBS symptoms, abdominal pain, constipation
Kruis (35)	1986	Wheat bran	15g	DB	16	Abdominal pain, Constipation
Manning (36)	1977	Wheat bran + high-fibre diet	20g	SB	6	Abdominal pain, Constipation
Snook (37)	1994	Wheat bran	36g	DB	7	Global IBS symptoms
Soltoft (38)	1976	Miller bran	30g	DB	6	Global IBS symptoms
Villigrassa (39)	1991	Wheat bran + high-fibre diet	20 + 10g	O	52	Abdominal pain, Constipation

DB: double-blinded trial; SB: single-blinded trial; O: open trial NA not applicable, 1 sachet is approximately 5 gram.

Figure 1. Comparison of different types of fibre and control treatment on global IBS symptom improvement.

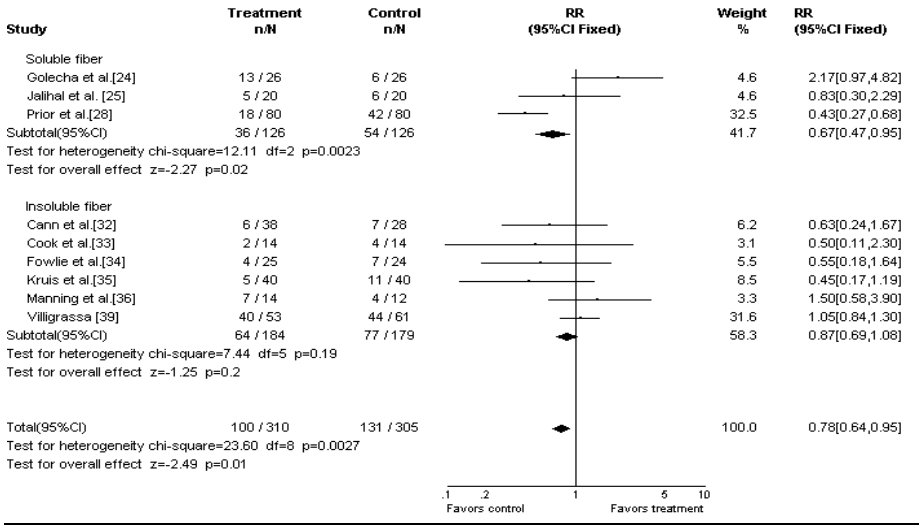


n: number of events in treatment or control group; N: number of participants in treatment or control group; RR: relative risk

Efficacy of soluble fibres

Of the seven studies (23-25,27-30) of ispaghula six found treatment favourable compared to placebo. IBS symptoms are not improved by psyllium therapy.(26) Calcium polycarbophil showed relief of global IBS symptoms and ease of stool passage. There was no significant improvement in either abdominal pain or bloating.(31) The combination high-fibre diet and ispaghula was not better than the combination high-fibre diet and placebo.(23) One study showed that ispaghula was more effective than wheat bran in the treatment of IBS.(30) Global IBS symptom improvement in patients treated with ispaghula was found in 5 of 7 studies.(25,27-30) Pooling the results showed the relative risk of global symptom relief to be 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 IBS patients, although it concerns only 2 studies (Figure 3).(25,28)

Figure 2. Comparison of different types of fibre and control treatment on IBS related abdominal pain.

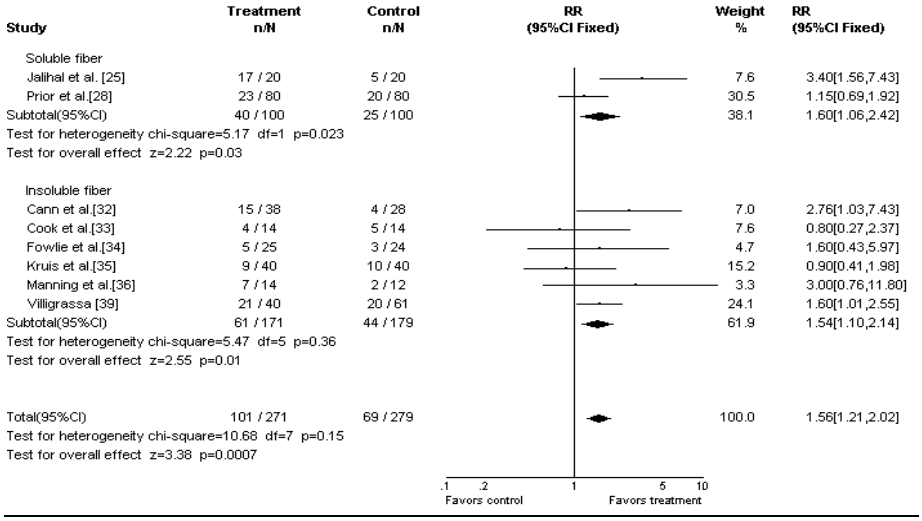


n: number of events in treatment or control group; N: number of participants in treatment or control group; RR: relative risk

Efficacy of insoluble fibre

In two of the six studies of wheat bran showed improvement in IBS symptoms.(32,36) Only one study of corn fibre found improvement in pain severity, stool frequency, and stool consistency, but there was no significant difference compared to placebo.(33) The single study found of miller bran found that IBS symptoms were not improved with miller bran compared to placebo.(38) None of the studies showed that bran was better than placebo on the outcome measure - global IBS symptom improvement - (Figure 1). In fact, global symptoms worsened with both insoluble fibre and placebo, but there was no significance difference between the two (RR 0.89 (95%CI: 0.72-1.11)). The six studies that reported on the outcome - 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 IBS patients with constipation, overall insoluble fibre (wheat bran) showed favourable results (RR 1,54 (95%CI: 1.10-2,14)) on this outcome measure (Figure 3).

Figure 3. Comparison of different types of fibre and control treatment on IBS related constipation.



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

Discussion

This systematic review shows that there is limited and conflicting evidence for the effectiveness of fibre in the treatment of IBS symptoms. For the measure efficacy - i.e. the proportion of patients with global IBS symptom improvement - fibre was significantly better than control. Fibre therapy also showed favourable results in IBS-related constipation. It might, however, increase abdominal pain in some IBS patients. However the effect of psyllium on constipation is based on only two studies: Jalihal (25) with 30 g and Prior (28) with approximately 5 g. Pooling with other studies with lower dosage might give an underestimation of the effects of a reasonable dose of psyllium.

The two types of fibre, soluble and insoluble, affected IBS symptoms differently. Soluble fibre was beneficial to global symptom improvement, while insoluble fibre was not more effective than placebo and might actually, in some IBS patients, worsen symptoms as compared to normal diet. In two studies a considerable effect was found. In one of these (25) a reasonable dose of psyllium was used. Toskes (29) used calcium polycarbophil which is a synthetic fibre resistant to bacterial degradation. Pooling of these studies with other psyllium studies that use less optimal doses underestimates the treatment effect.

Evidence for the effectiveness of soluble fibre was concluded from the pooled results. IBS patients treated with this type of fibre reported 1.3 times more global improvement than their controls. The effect of soluble fibre on IBS-related abdominal pain, however, is controversial. In fact, the studies that reported on the outcome “relief of abdominal pain” varied considerably in this measure and showed conflicting results.(24,25,28)

The efficacy of insoluble fibre in the treatment of IBS patients is also controversial. The studies showed that diets with a large amount of insoluble fibres might actually be worse than a normal diet. The clinical improvement of IBS patients treated with insoluble fibres was not better than treatment with placebo.(33,34,37,38)

The outcomes used in each of the randomised 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 quality of life, were not used in any of the trials. Both on global IBS symptom and on symptom improvement the studies showed heterogenic results. The main reason for this may be caused by the small sample sizes, 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 a double-blind assessment should be used for in IBS trials.(40) However, many difficulties are encountered in designing and executing trials with dietary intervention. Since blinding in trials

evaluating a high-fibre dietary advice is difficult, we accepted these studies with the best possible methodology available.

We had to exclude three studies from our analysis, as no data could be extracted to calculate a relative risk. None of these showed a positive response of treatment. This might have given rise to an overestimation of the effectiveness of fibre.

The majority of patients with IBS is 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. Primary care IBS patients may, in fact, respond differently than referred patients to dietary therapy.(41) Furthermore, primary care patients who respond to treatment with bulking agents are less likely to be referred to a hospital clinic. On top of this more than half of the symptomatic "patients" from the general population do not even present to their GP. The efficacy of fibre in this population is unknown.

The role of fibre in the pathophysiology of IBS remains poorly understood.(42) An increase in the amount of dietary fibre is an almost universal recommendation in the primary care management of IBS(3,5) and guidelines on IBS management for out-clinic patients advise the increase of 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 effectiveness of fibre therapy in IBS 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 IBS-related abdominal pain. Soluble and insoluble fibres have a different effect on global IBS symptoms. Insoluble fibre is probably not better than placebo and might, in some patients, even worsen the clinical outcome. For the development of evidence-based management guidelines, valid clinical studies in primary care patients, that focus on the effectiveness and tolerability of soluble and insoluble fibres, 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-II47.
2. Drossman DA, Whitehead WE. Irritable bowel syndrome: a technical review for practice guideline development. Gastroenterol 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. Gastroenterol 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, England: The Cochrane Collaboration, 2000.
20. Arfmann S, Andersen JR, Hegnhoj 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. Gastroenterol 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(suppI):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. Alim Pharm 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;(Suppl II)47:ii1-ii19.

Chapter 8

Dietary interventions in irritable bowel syndrome: soluble, insoluble or no fibre? A randomised controlled trial in primary care

Bijkerk CJ, de Wit NJ, Muris JWM, Whorwell PJ, Knottnerus JA, Hoes AW.
Submitted for publication.

Abstract

Background: Although increasing dietary fibre is almost universally advocated for the treatment of irritable bowel syndrome (IBS) there has never been a trial assessing its effects in the primary care setting. Furthermore there have been no formal comparisons of soluble versus insoluble fibre in this condition. We assessed the effectiveness of increasing the dietary content of soluble (psyllium) or insoluble fibre (bran) in a randomised, placebo controlled trial in primary care.

Methods: 275 IBS patients were randomly allocated to 12 weeks treatment with either 10 grams of soluble fibre (psyllium) (n=85) or 10 grams of insoluble fibre (bran) (n=97) or 10 grams of placebo (rice flour) (n=93).The primary outcome measure was the global assessment of adequate relief of symptoms. Secondary endpoints included changes in IBS symptom severity and quality of life. Statistical analyses were based on the intention-to-treat principle. A worst-case analysis was performed to deal with loss-to-follow-up.

Findings: The proportion of patients with adequate relief was significantly greater in the psyllium group than in the placebo groups after 1 month (57% v 34.6%, RR 1.60 (95%CI: 1.13-2.26)) and 2 months of treatment (59% v 41%, RR 1.44 (95%CI: 1.02-2.06)). During the third month the difference between psyllium and placebo (46.3% v 32.1%) was not statistically significant (RR 1.36 (95%CI: 0.90-2.04). These findings were similar in the worst case-analysis. Bran was more effective as compared to placebo after 3 months of treatment only (32.0% v 19.4%, RR 1.70 (95%CI 1.12-2.57)) but this was no longer statistically significant in the worst case analysis (RR 1.45 (95%CI: 0.97-2.16)). After 3 months of treatment the mean symptom severity reduction in the psyllium group was 90 points, versus 49 points in the placebo group (p=0.03). No differences were found with respect to quality of life in the three groups.

Interpretation: Psyllium offers benefit in IBS patients in primary care, whereas bran should only be recommended with caution.

Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterised by recurrent episodes of abdominal pain or discomfort associated with an altered bowel habit, not explained by any structural or biochemical changes in the gut.(1) The population prevalence of IBS is in the order of 10% and approximately a quarter of those with IBS symptoms seek medical advice.(2) Most studies report a female preponderance and the reported incidence of IBS in primary care is 4-13/1000 patients per year with less than 5% of these being referred to hospital.(3) IBS is a chronic recurrent condition with relapsing symptoms in more than half of the patients.(4) IBS should not be diagnosed by exclusion, but preferably as a "positive" diagnosis. Diagnostic tools such as the Rome criteria have been developed to facilitate this. The Rome criteria are primarily designed for research purposes and their validity in clinical primary care is not well established. The majority of the GPs is not familiar with their use.(5-8)

In the management of IBS dietary advice is frequently given. The majority of GPs recommends an increase in the fibre content of the daily diet, through the addition of insoluble fibre in the form of bran.(9) Furthermore, approximately half of the IBS patients receives pharmacotherapy which frequently includes psyllium based supplements.(7) However, the evidence that fibre actually alleviates IBS symptoms is limited, and insoluble fibre may even exacerbate IBS symptoms.(10) In addition, much of the available studies suffer from methodologic weaknesses and all the trials assessing the effectiveness of fibre in IBS have been conducted in secondary care.(11) In contrast most patients are treated in primary care, and there are indications that the latter group benefits more from fibre treatment than the referred group.(3;9;12;13)

We conducted a randomised, placebo controlled trial in primary care patients with IBS to assess the effectiveness of three months treatment with either soluble (psyllium) or insoluble (bran) fibre on symptoms and quality of life.

Methods

Patients

Patients were recruited in the practices from the Utrecht and Maastricht primary care research networks. GPs in both networks have vast experience in participating in clinical trials in primary care. Patients between 18-65 years who were diagnosed with IBS in the past two years were selected from the medical electronic files of the participating practices using the International classification of health problems in primary care (ICPC)(14) code D93 (irritable bowel syndrome), or the text words

('IBS', ''or spastic colon'). The selected patients received an invitational letter signed by their GP to participate in the trial. Non-responding patients received one reminder. In addition to these 'prevalent' IBS patients, also patients consulting their GP with a new onset IBS during the inclusion period ('incident' IBS patients) were invited to participate.
Patients with IBS symptoms during the past 4 weeks with either (a) 'definite' IBS, according to the Rome II diagnostic criteria, or (b) 'probable' IBS, pragmatically diagnosed by their GP were eligible for inclusion. Patients with an organic explanation for their bowel symptoms, those with severe psychosocial disturbance and psychiatric disorders (i.e. panic disorder, generalized anxiety disorder and mood disorder), those under specialist treatment for IBS in the last 2 years and those not mastering the Dutch language were excluded. Written informed consent was obtained from all patients. The inclusion period lasted from April 2004 to October 2006.

Randomisation
After inclusion and signing of informed consent, patients were randomly allocated to one of two active treatment groups or placebo by means of a six block random number tables procedure. The randomisation list was produced by the pharmacy of the University Medical Center Utrecht. The treatment allocation was determined at the baseline visit by the practice nurse by drawing a sealed envelope.

Treatments
Patients were randomly allocated to a 12-week treatment regime with either (a) 10 gram soluble fibre (psyllium) (b) 10 gram insoluble fibre (wheat bran) or (c) placebo (rice wheat) in 2 daily doses, to be taken with the meal. The average intake of dietary fibre in an adult Dutch population aged 25 to 65 years is estimated to be 24.0 +/- 6.9 gram per day (mean +/- SD), or 10.5 +/- 2.6 gram per 1,000 kcal. An addition of 10 gram fibre to the diet (total dietary fibre content 30-40 gram), is usually considered adequate.(7;15) The dietary supplements were delivered in identical containers by the practice nurse at monthly study visits. The study was blinded at three levels (patient, doctor and research personnel), but the practice nurse was aware of the treatment allocated. All participants were instructed not to change dietary habits, and to take sufficient fluids per day.

Outcome assessment and follow-up
Patients were instructed to visit their GP 1, 2 and 3 month after the baseline visit (figure 1). In addition, they were asked to keep a diary during the 3 months of treatment to assess the primary endpoint and measure treatment compliance. In line

with previous recommendations for outcome assessment in functional GI disease research, we chose the Adequate Relief question ("Did you have adequate relief of IBS-related abdominal pain or discomfort in the past week?") as the primary outcome.(16;17) This instrument is a validated and generally accepted simple outcome assessment for IBS treatment. Patients experiencing more than 2 weeks of adequate relief per month were considered a responder.(18) Secondary outcome measurements included IBS symptom severity and quality of life. Symptom severity was assessed with the IBS symptom severity score (IBS SSS). This is a thoroughly validated IBS symptom score, which relates five aspects of bowel dysfunction to the actual intensity of IBS symptoms, using visual analogue scales.(19) Disease-specific quality of life was monitored with the Irritable Bowel Syndrome Quality of Life scale (IBS QOL), which includes 30 items in nine subscales, and has been validated in various populations.(20) Fibre intake was monitored every 4 weeks during the trial using a Food Frequency Questionnaire including 78 items on fibre intake and 24 on fluid intake. The questionnaire is a self-administered food frequency questionnaire validated for ranking subjects according to intake of dietary fibre and was adapted from the EPIC Food Frequency Questionnaire.(21;22) The primary outcome was measured on a weekly basis. The secondary outcomes were recorded at the schedules follow-up visits to the general practitioner, after 1, 2 and 3 months. Compliance with the trial medication was checked every visit by scrutinising the patient's diary.

Power calculation

We considered a minimal difference of 20% in the proportion of responders on the adequate relief scale (i.e. more than 2 weeks Adequate Relief per 4 weeks) between the active treatments and placebo as clinically relevant. The prior placebo response was estimated at 40%.(17) Thus, 86 patients were required per treatment arm (total 258 patients) to give the study 80% power with a type I error of 5%. Assuming a dropout of 10%, we aimed to include 285 IBS patients.

Statistical analysis

We analysed the data using SPSS for windows 12.0.1 (SPSS, Inc. Chicago, Illinois, USA). Statistical analyses were based on the intention-to-treat principle. The proportion responders in three groups were calculated and compared at 1, 2 and 3 months. Relative risks (RR) with 95% confidence intervals (CI) and risk differences (RD) with 95%CI compared to placebo were calculated. Similar calculations were made after imputing missing values on the primary outcome, assuming that patients who not fill in the adequate relief question in the diary were non-responders ("worst-case analysis"). The secondary outcomes IBS Symptom Severity Score and IBS

Quality of Life after 1, 2 and 3 months were compared with the score at baseline (t=0). Stability of the treatment effect in time was assessed using one-factorial ANOVA for repeated measures. To correct for possible differences in relevant baseline characteristics between the three groups we performed multiple regression analyses. As pre-specified in the study protocol, subgroup analysis was performed on patients fulfilling the Rome II IBS diagnostic criteria and on those with constipation predominant IBS.

Results

Patients

A total of 296 patients agreed to participate in the trial: 193 'prevalent' IBS patients and 103 'incident' IBS patients. For various reasons (second thoughts, non eligibility or no time) 21 patients did not attend the baseline visit. In total 275 patients were randomised; 85 were allocated to psyllium, 97 to bran and 93 patients to placebo. Most of the patients were Caucasian (94%) and female (78%) and the mean age was 34.4 years (SD 10.9). In 25% of the patients IBS was diagnosed within the preceding two years and 39% fulfilled the Rome II criteria for IBS. More than half (56%) of the patients had constipation predominant IBS. The mean dietary fibre intake before participation was 26.9 gram/day (SD 11.8) and patients used on average 2.4 litre fluids/day (SD 1.0). At baseline patients allocated to psyllium reported less severe IBS abdominal pain as compared to the bran and placebo group. The treatment groups did not differ with respect to other patients' characteristics (table 1).

Table 1. Baseline characteristics

Characteristic	Psyllium (n=85)	Bran (n=97)	Placebo (n=93)
	%	%	%
Mean age, years (sd)	34.6 (10.2)	34.3 (11.7)	35.2 (18.2)
Gender			
Female	75.0	75.8	83.0
Ethnic origin			
Caucasian	92.9	92.6	96.6
Duration of IBS symptoms			
< 2 years	22.4	32.6	19.3
2-5 years	31.8	25.3	20.5
5-10 years	15.3	17.9	20.5
> 10 years	30.6	24.2	39.8

Table 1. Continued

Characteristic	Psyllium (n=85)	Bran (n=97)	Placebo (n=93)
	%	%	%
Rome II IBS	41.2	40.0	35.6
IBS subtype			
IBS with constipation	52.9	57.7	58.1
IBS with diarrhoea	29.1	18.6	26.9
IBS with alternating	17.6	23.7	16.5
IBS symptoms (mean (sd))			
Severity of abdominal pain (0-100)	42.8 (29.3)	53.8 (31.6)	55.1 (36.9)
IBS SSS score (0-500)	262 (68.0)	270 (77.2)	279 (69.7)
IBSQOL (0-100)	72.1 (16.1)	73.6 (15.8)	73.8 (15.1)
Dietary intake (mean (sd))			
Fibres (g/day)	28.0 (12.1)	27.6 (14.5)	27.2 (15.0)
Fluids (l/day)	2.3 (1.0)	2.4 (1.0)	2.4 (1.0)

Follow-up

Two hundred and thirty-four (85.0%) patients attended the second visit at one month, 195 (72.0%) the visit at two months and 164 (60.0%) attended the final visit at the end of the 3 months treatment period (figure 1). In total 111 patients (40.4%) were lost to follow-up during the treatment period: 31 (26.4%) in the psyllium group, 43 (44.4%) in the bran group and 37 (40.0%) in the placebo group. Reasons were non-medical (e.g. moved to another city, n=15), presumed lack of benefit (n=10), symptom free (n=2) and unknown (n=52). In total 34 patients did not complete the trial due to intolerance for the trial medication: seven patients allocated to the psyllium, 18 patients allocated to bran, and 9 patients allocated to placebo. Patients who completed the trial and those lost to follow-up did not significantly differ with respect to demographic and disease specific characteristics (data not shown).

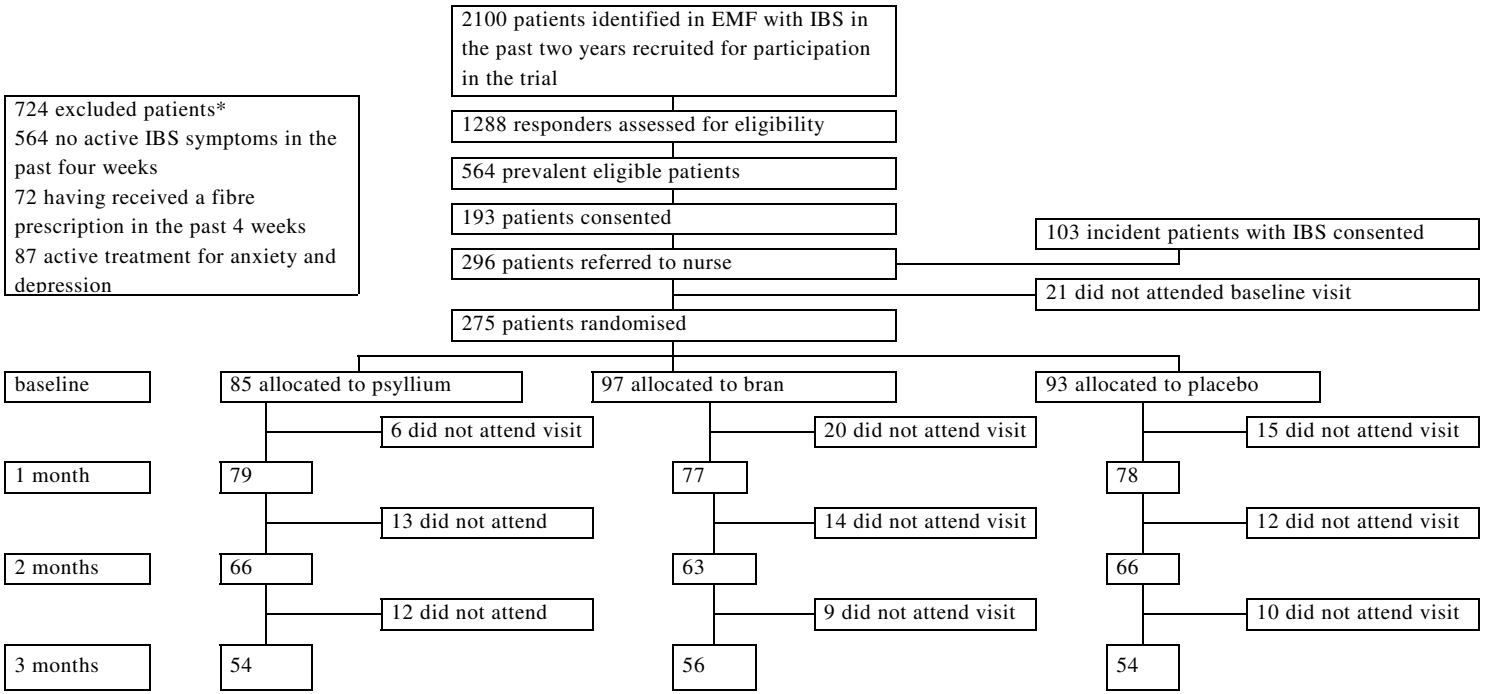


Figure 1. Trial profile, IBS= irritable bowel syndrome, EMF= electronic medical file, GP= general practitioner. None of the patients assigned to psyllium, bran or placebo received different treatment. *number exceeds 724 because more than one reason could be indicated

Primary outcome

Responder rates were significantly higher with psyllium than placebo during the first month of treatment (RR 1.60 (95%CI: 1.13-2.26)) with a risk difference of 22.4%; the number needed to treat being 4 (i.e. for every four patients who receive psyllium one reported at least 50% adequate relief of abdominal pain or discomfort during one month of treatment). A similar positive effect was observed during the second month of treatment (59% v 41%, RR 1.44 (95%CI: 1.02-2.06)). During the third month the difference between psyllium and placebo (46.3% v 32.1%) was not statistically significant (RR 1.36 (95%CI 0.90-2.04)). Only during the last month of treatment bran was more effective than placebo (57% v 32%, RR 1.70 (95%CI: 1.12-2.57)) (table 2a). Figure 2 shows the proportion of patients in each group with adequate relief per week.

In the worst-case analysis (i.e. considering patients lost to follow-up as non-responders) psyllium remained more effective than placebo during the first two treatment months, but the effect of bran compared to placebo during the third month was no longer statistically significant (RR 1.45 (95%CI: 0.97-2.16) (table 2b).

Analysis restricted to those patients fulfilling the Rome II criteria for IBS showed larger responder rates for psyllium versus placebo (e.g. in the first month RR 1.81 (95%CI 1.12-2.94)) compared to 1.60 in all IBS patients).

A subgroup analysis for IBS patients with constipation showed comparable results. For example, after 1 month of treatment psyllium was better than placebo: RR 1.65 (95%CI 1.05-2.62)).

Table 2A. Adequate relief of abdominal pain or discomfort (at least 2 weeks every month) ITT analysis

Follow up assessment	Treatment	Responder		RR (95% CI)	Treatment difference (95% CI)	NNT
Month		N/N	%		%	
1	Psyllium	45/79	57.0	1.60 (1.13-02.26)	22.4 (0.07-0.38)	4.5
	Bran	31/77	40.3	1.13 (0.81-1.58)	5.7 (-0.10-0.21)	17.5
	Placebo	27/78	34.6	-	-	-
2	Psyllium	39/66	59.1	1.44 (1.02-2.06)	18.2 (0.14-0.35)	5.5
	Bran	32/63	50.8	1.22 (0.86-1.72)	9.9 (-0.07-0.27)	10.1
	Placebo	27/66	40.9	-	-	-
3	Psyllium	25/54	46.3	1.36 (0.90-2.04)	14.2 (-0.04-0.32)	7.0
	Bran	31/54	57.4	1.70 (1.12-2.57)	25.3 (0.73-0.43)	4.0
	Placebo	18/56	32.1	-	-	-

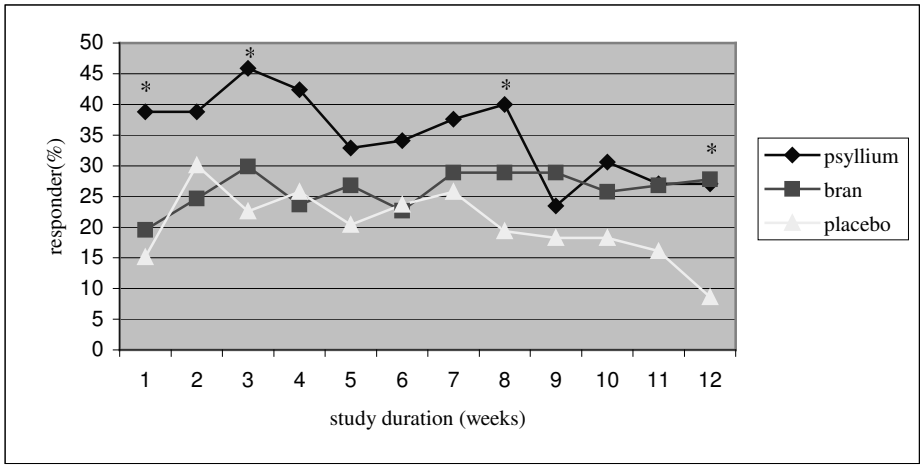
NNT, number needed to treat

Table 2B. Adequate relief of abdominal pain or discomfort (at least 2 weeks every month) ITT analysis with imputation of missing data as non-responders (worst-case analysis)

Follow up assessment	Treatment	Responder		RR (95% CI)	Treatment difference (95% CI)	NNT
Month		N/N	%		%	
1	Psyllium	45/85	52.9	1.66 (1.19-2.31)	20.9 (0.10-0.38)	4.2
	Bran	31/97	32.0	1.07 (0.78-1.49)	3.0 (-0.10-0.16)	33.3
	Placebo	27/93	29.0	-	-	-
2	Psyllium	39/85	45.9	1.44 (1.04-2.00)	16.9 (0.03-0.31)	5.9
	Bran	32/97	33.0	1.10 (0.80-1.53)	4.0 (-0.09-0.17)	25.0
	Placebo	27/93	29.0	-	-	-
3	Psyllium	25/85	29.4	1.32 (0.91-1.95)	10.0 (-0.03-0.23)	10.0
	Bran	31/97	32.0	1.45 (0.97-2.16)	12.6 (0.003-0.25)	7.9
	Placebo	18/93	19.4	-	-	-

NNT, number needed to treat

Figure 2. Proportion of patients with adequate symptom relief per week



* p<0.05

Secondary outcomes and compliance

The reduction of symptom severity in the psyllium group was higher than in the placebo group with a significant mean reduction of 90 versus 49 points, (p=0.03) during the third month of treatment, whereas the change in symptom severity in the bran group was comparable to the placebo group. There were no significant differences between the three groups with respect to changes in the severity of IBS related abdominal pain or quality of life (table 3).

The compliance with the trial medication did not differ between the psyllium and bran group. Patients allocated to psyllium added on average daily 7.1 grams (SD

3.1), bringing their total dietary fibre intake to 35.1 gram/day (SD 14.9). Patients allocated to bran added on average 6.5 gram/day (SD 3.3) and received 34.1 grams dietary fibre/day in total (SD 17.2). The fibre intake in the daily diet, as monitored with the Food Frequency Questionnaire did not change during the treatment period. Also, the total fluid intake, on average 2.5 litre/day (SD 0.8) did not differ between the groups.

Table 3. Change in IBS symptom severity, severity of abdominal pain and quality of life from baseline by month

Follow-up assessment	Treatment	Absolute and relative change in IBS SSS score (0-500)			Absolute and relative change in severity of abdominal pain score (0-100)			Absolute and relative change in IBSQOL (0-100)		
Month		Mean	%	P	Mean	%	P	Mean	%	P
1	Psyllium	-69.1	26.3	0.19	-8.1	18.9	0.95	4.8	6.7	0.95
	Bran	-60.5	22.4	0.47	-12.1	22.5	0.61	3.6	4.9	0.93
	Placebo	-49.3	17.7	-	-8.5	15.4	-	2.7	3.7	-
2	Psyllium	-69.2	26.4	0.92	-10.3	24.1	0.58	6.0	8.1	0.58
	Bran	-52.9	19.6	0.32	-10.5	19.5	0.63	5.2	7.1	0.85
	Placebo	-70.8	25.4	-	-14.4	26.1	-	5.1	6.9	-
3	Psyllium	-89.5	34.2	0.03	-13.8	32.2	0.79	7.3	10.1	0.79
	Bran	-58.0	21.5	0.61	-11.5	21.4	0.98	3.9	5.3	0.07
	Placebo	-48.9	17.5	-	-11.7	21.2	-	4.3	5.8	-

Tolerability

63 of 85 (74.1%) patients in the psyllium group and 62 of 97 (63.9%) patients in the bran group and 61 of 93 (65.9%) patients in the placebo group reported at least one adverse event of moderate severity during the study (table 4). Diarrhoea and constipation were the most commonly reported adverse events. The proportions of patients with diarrhoea and constipation in the psyllium and bran groups were comparable with placebo. Severe constipation was reported in one patient treated with bran. No serious adverse events were reported during the study.

Table 4. Most frequent adverse effects of moderate severity, regardless of study drug relation

	Psyllium (n=85)		Bran (n=97)		Placebo (n=94)		
Adverse effect	N	%	N	%	N	%	P
Diarrhoea	50	61.7	59	62.8	62	71.3	0.35
Constipation	51	62.2	53	57.6	59	69.4	0.26
Nausea/Vomiting	12	14.1	20	21.1	18	19.6	0.46
Dysphagia	9	10.6	17	17.9	12	13.0	0.35
Backache	41	48.2	41	43.2	40	43.5	0.63
Headache	28	32.9	36	37.9	29	31.5	0.75
Fatigue	30	35.3	35	36.8	34	37.4	0.96
Flatulence	59	71.1	68	74.7	70	77.8	0.60
Heartburn	23	27.7	26	28.6	22	24.4	0.81
Lower urinary tract symptoms	33	39.8	46	50.5	39	43.3	0.34
Pelvic pain	9	10.8	15	16.5	18	20.0	0.25
Muscle or joint pain	38	45.8	37	40.7	42	47.2	0.65

Discussion

In this randomised trial in primary care IBS patients, psyllium resulted in a significantly greater proportion of IBS patients reported adequate symptom relief as compared to placebo supplementation. In addition patients on psyllium also experienced a significantly larger reduction in IBS symptom severity. There were no significant differences between the treatment groups in abdominal pain or health related quality of life. In contrast, bran showed no clinically relevant benefit, while many patients appear to be intolerant for bran.

To our knowledge this is the first randomised controlled trial in primary care assessing the effects of fibre in the treatment of IBS. At baseline the three treatment groups were comparable with the exception of a somewhat lower symptom severity in the psyllium group. However, adjustment for baseline symptom severity in the multivariate analysis only increased the observed beneficial effect; e.g. the 1 month relative risk for adequate in the psyllium versus the placebo was 2.70 (95%CI 1.33-5.46).

We allowed all patients with a diagnosis of IBS according to their GP to participate in the study in order to optimize the applicability of the results to primary care clinical practice. A sizeable proportion (61%) of our patients did not fulfil the Rome II criteria. Subgroup analysis demonstrated that there was a clinically relevant effect in either those fulfilling or not fulfilling the Rome II criteria, albeit that, as may be expected, the benefit was somewhat greater in the former group. The Rome criteria

for IBS have been developed mainly for research purposes and it is noteworthy that they are infrequently used in primary care (5-8).

Successful blinding of dietary interventions in research is difficult to achieve, but maximum precautions were taken to guarantee that the treatment looked identical concerning packaging and content. Clinical staffs involved were kept blinded for treatment allocation throughout the study. However, in retrospect approximately three quarters of patients correctly guessed which treatment they were given. There is no clear explanation for this. It seems unlikely that the appearance or the taste of the treatment was the reason, but they may have recognized the effect of soluble or insoluble fibre supplements from previous experience. For instance, a fibre supplement might produce a greater sense of bloating than rice flour.

Forty percent of the patients in this study stopped participation before the final visit. The main reason was that they felt worse by taking the fibre supplement. Although this drop-out rate is considerable, it is comparable to that in other trials of this nature.(23-25) The motivation of patients to participate rapidly drops when an intervention is too cumbersome or time consuming, especially when it does not lead to any immediate effect or is difficult to tolerate. Obviously, a high drop out rate is going to contribute negatively to the overall result of the study especially when these patients are classified as treatment failures. Although this "worst case scenario" is the most appropriate way of analysing treatment effectiveness it may underestimate the true effectiveness of fibre treatment.(17)

The drop-out rate was highest among those patients randomised to bran, and this mainly occurred during the first month of treatment. This was mainly attributed to worsening of IBS symptoms. This has also been reported in secondary care.(11) This is supported by the finding the number of patients stopping treatment intake because of intolerance was twice as high in the bran group as those in the psyllium or placebo group. Probably, those left in the trial taking bran were a small subset of patients who responded well to this supplement, as is also indicated by the comparable adverse event rates reported in the three groups.

Our findings regarding the effectiveness of psyllium are in line with the conclusion from a meta-analysis we published earlier. However, in that systematic review we concluded that most of the studies had methodological limitations, such as inadequate outcome assessments and considerable patient heterogeneity. In this trial we tried to overcome many of these shortcomings, and in addition focused on primary care patients, where the vast majority of IBS patients is managed.

In conclusion, the results of this large scale trial in primary care trial support the addition of soluble fibre, such as psyllium, but not bran as an effective first treatment approach in the clinical management of IBS.

Contributors

All authors contributed to the design of the trial, interpretation of the results and writing of the manuscript. C.J. Bijkerk contributed to the recruitment of co-operating general practitioners, data collection, management of the trial, and statistical analysis, N.J. de Wit recruited general practitioners and co-coordinated the trial, J.W.M. Muris recruited general practitioners, P.J. Whorwell and J.A. Knottnerus contributed to the statistical analysis and A.W. Hoes co-coordinated the trial. All authors met regularly as a steering group.

Conflict of interest statement

We declare that we have no conflict of interest

Acknowledgements

We thank all participating patients, our colleagues, assistants and nurses in the participating practices without whom this study could not have been carried out. We thank B. Slotboom for his valuable in constructing the datafile and P. Zuithoff for statistical advice. The study was undertaken in accordance with the European statement for good clinical practice, which includes the provisions of the declaration of Helsinki of 2000. The medical ethics committee of the Utrecht University Medical Center approved the study protocol. The trial was registered at www.clinicaltrials.gov (NCT00189033). This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw number 4200.0020). The psyllium for this study was delivered by Pfizer B.V. the Netherlands.

References

1. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006 Apr;130(5):1480-91.
2. Jones R, Lydeard S. Irritable bowel syndrome in the general population. BMJ 1992 Jan 11;304(6819):87-90.
3. Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: prevalence, characteristics, and referral. Gut 2000 Jan;46(1):78-82.
4. Ruigomez A, Wallander MA, Johansson S, Garcia Rodriguez LA. One-year follow-up of newly diagnosed irritable bowel syndrome patients. Aliment Pharmacol Ther 1999 Aug;13(8):1097-102.
5. Mearin F, Badia X, Balboa A, Baro E, Caldwell E, Cucala M, et al. Irritable bowel syndrome prevalence varies enormously depending on the employed diagnostic criteria: comparison of Rome II versus previous criteria in a general population. Scand J Gastroenterol 2001 Nov;36(11):1155-61.
6. Vandvik PO, Aabakken L, Farup PG. Diagnosing irritable bowel syndrome: poor agreement between general practitioners and the Rome II criteria. Scand J Gastroenterol 2004 May;39(5):448-53.
7. Janssen HA, Borghouts JA, Muris JW, Metsemakers JF, Koes BW, Knottnerus JA. Health status and management of chronic non-specific abdominal complaints in general practice. Br J Gen Pract 2000 May;50(454):375-9.
8. Oberndorff-Klein Woolthuis AH, Brummer RJ, de Wit NJ, Muris JW, Stockbrugger RW. Irritable bowel syndrome in general practice: an overview. Scand J Gastroenterol Suppl 2004;(241):17-22.
9. Bijkerk CJ, de Wit NJ, Stalman WA, Knottnerus JA, Hoes AW, Muris JW. Irritable bowel syndrome in primary care: the patients' and doctors' views on symptoms, etiology and management. Can J Gastroenterol 2003 Jun;17(6):363-8.
10. Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. Lancet 1994 Jul 2;344(8914):39-40.
11. Bijkerk CJ, Muris JW, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2004 Feb 1;19(3):245-51.
12. Longstreth GF, Hawkey CJ, Mayer EA, Jones RH, Naesdal J, Wilson IK, et al. Characteristics of patients with irritable bowel syndrome recruited from three sources: implications for clinical trials. Aliment Pharmacol Ther 2001 Jul;15(7):959-64.

13. van der Horst HE, van Dulmen AM, Schellevis FG, van Eijk JT, Fennis JF, Bleijenberg G. Do patients with irritable bowel syndrome in primary care really differ from outpatients with irritable bowel syndrome? Gut 1997 Nov;41(5):669-74.
14. Classification Committee of WONCA. ICHPPC-2 defined. International classification of health problems in primary care. Oxford: Oxford University Press; 1983.
15. Van Staveren WA, Hautvast JG, Katan MB, Van Montfort MA, Van Oosten-Van Der Goes HG. Dietary fiber consumption in an adult Dutch population. J Am Diet Assoc 1982 Apr;80(4):324-30.
16. Bijkerk CJ, de Wit NJ, Muris JW, Jones RH, Knottnerus JA, Hoes AW. Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics. Am J Gastroenterol 2003 Jan;98(1):122-7.
17. Irvine EJ, Whitehead WE, Chey WD, Matsueda K, Shaw M, Talley NJ, et al. Design of treatment trials for functional gastrointestinal disorders. Gastroenterology 2006 Apr;130(5):1538-51.
18. Mangel AW, Hahn BA, Heath AT, Northcutt AR, Kong S, Dukes GE, et al. Adequate relief as an endpoint in clinical trials in irritable bowel syndrome. J Int Med Res 1998 Mar;26(2):76-81.
19. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther 1997 Apr;11(2):395-402.
20. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. Dig Dis Sci 1998 Feb;43(2):400-11.
21. Ocke MC, Bueno-de-Mesquita HB, Goddijn HE, Jansen A, Pols MA, Van Staveren WA, et al. The Dutch EPIC food frequency questionnaire. I. Description of the questionnaire, and relative validity and reproducibility for food groups. Int J Epidemiol 1997;26 Suppl 1:S37-S48.
22. Ocke MC, Bueno-de-Mesquita HB, Pols MA, Smit HA, Van Staveren WA, Kromhout D. The Dutch EPIC food frequency questionnaire. II. Relative validity and reproducibility for nutrients. Int J Epidemiol 1997;26 Suppl 1:S49-S58.
23. Parisi G, Bottona E, Carrara M, Cardin F, Faedo A, Goldin D, et al. Treatment effects of partially hydrolyzed guar gum on symptoms and quality of life of patients with irritable bowel syndrome. A multicenter randomized open trial. Dig Dis Sci 2005 Jun;50(6):1107-12.

24. Rees G, Davies J, Thompson R, Parker M, Liepins P. Randomised-controlled trial of a fibre supplement on the symptoms of irritable bowel syndrome. J R Soc Health 2005 Jan;125(1):30-4.
25. Snook J, Shepherd HA. Bran supplementation in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 1994 Oct;8(5):511-4.

Chapter 9

General discussion

Case history

A 27 year-old young secretary visited her general practitioner (GP) with recurrent episodes of abdominal pain in the left side of the belly, bloating and altered bowel habits. The GP could not find evidence for an organic explanation for her complaints and a diagnosis of irritable bowel syndrome (IBS) was established. The patient was counselled and was given lifestyle advice mainly focussing on increasing the fibre content of her daily diet. Four weeks later, she returns to the practice because, after she added wheat bran to the diet, her bowel complaints became even worse. "Doctor, please do advice me on what is best for my bowels so that I get rid of my complaints. I don't know how to cope with it anymore." The GP told her that in general there are hardly any effective drugs for IBS. However, he just read the results of a recent trial on the effectiveness of treatment with dietary fibre in patients with IBS, concluding that psyllium, in contrast to bran, can effectively reduce symptoms of abdominal pain and/or discomfort. The GP suggested the patient to add psyllium fibres, to the daily diet with sufficient fluid intake. Four weeks after the start of the therapy, the patient reports back to the GP, telling him that she had experienced adequate relief of abdominal pain and discomfort.

In this chapter we will discuss the main outcomes of the studies presented in this thesis, provide recommendations for management of patients with irritable bowel syndrome (IBS) in primary care and suggest directions for future research.

The main conclusions of our studies on the management of IBS patients in primary care are:

1. Patients and doctors in primary care generally agree on IBS symptomatology and consider pain and bloating as its main features.
2. Consultation frequency is mainly driven by the severity of IBS symptomatology, rather than by its impact on quality of life or psychological distress.
3. Irritable bowel syndrome is associated with a high prevalence of comorbidity. Before the diagnosis the prevalence of comorbidity is comparable to that in a random age and sex matched sample of patients from primary care. All comorbidity is more frequent in the year of the IBS diagnosis. The prevalence of somatic comorbidity drops afterwards, while functional and psychiatric disorders remain highly prevalent. Patients with such comorbidity might need tailored approaches in treatment.

4. The subjective measurement "adequate relief of abdominal pain or discomfort" is currently the best choice for the outcome assessment in IBS research. In addition, an integrated IBS symptom scale may be used as a secondary outcome measure, of which the IBS Symptom Severity Scale (IBS SSS) is presently the best available instrument. Finally, the IBS Quality of Life score (IBS-QOL) is the preferred scale to assess changes in health-related quality of life.
5. Based on recruitment analysis of our randomised controlled trial (RCT) we conclude that patients randomised in IBS research differ from eligible IBS patients with respect to type and intensity of symptoms and disease history. This might influence the applicability of the trial results.
6. Soluble and insoluble fibres confer distinct effects in IBS. Soluble fibre (psyllium) is more effective than placebo in reducing IBS symptoms, whereas insoluble fibre (bran) should only be recommended with caution. Psyllium seems the preferred treatment in IBS patients.

Rational IBS management in primary care

The diagnostic process in primary care; symptom-based or guided by the patient's profile?

Diagnosing IBS implies - like in many other functional disorders - balancing between a positive symptom-based diagnosis and exclusion of other organic gastrointestinal disease through a diagnostic work-up. The GP is the first physician confronted with this challenge, and also the one to "set the tune". Several factors influence this balance: the likelihood of organic disease, the presence of alarm symptoms, the need for prevention of somatisation, the presence of comorbidity and psychosocial factors, and the doctor's or patient's need for diagnostic confirmation.

Although patients and GPs agree on the predominant symptoms in IBS, and consider abdominal pain and bloating as its main features, primary and secondary care physicians diagnose IBS differently.(1) We demonstrated that GPs do not use the strict consensus-based diagnostic criteria that are commonly adopted in secondary care. In our study, only one third of the primary care patients diagnosed with IBS did fulfill the strict Rome definition of more than 3 months of abdominal pain during the previous year. Yet the treatment effect in our study did not differ between those IBS patients who met the Rome criteria and those who did not. GPs are obviously able to identify IBS patients with confidence, but how do they diagnose IBS in daily practice?

Basically, general symptoms such as 'abdominal pain' or 'bloating' trigger the diagnosis. Additional symptoms, such as constipation, diarrhoea and flatulence or dyspepsia, may support the diagnosis. The predominant IBS symptoms may differ

per culture.(2) Obviously one of the key differences with the diagnostic process suggested by the Rome group is that GPs do not use a strict time window. While the Rome criteria require the presence of symptoms during at least a year, GPs diagnose IBS even in patients with a much shorter disease history. In recent primary care guidelines on diagnosing and management of IBS patients, it was concluded that a definition including symptoms such as abdominal pain or discomfort, bloating, and alteration in bowel habit, for at least 4 weeks would be more applicable in general practice.(2)

In addition to symptoms the primary care diagnosis of IBS is guided by the "patient's profile". GPs are aware of the fact that women are more likely to have IBS and recognise family patterns of IBS through generations. Characteristics that support this "IBS profile" include high consultation patterns, a recent major life event, increased prevalence of psychiatric and somatic comorbidity and a history of medically unexplained physical symptoms in the past. One of the essential differences between the diagnostic process in primary and secondary care is that - because of their long-term relation with the patient - GPs are aware of most of the characteristics determining this patient profile.

Diagnosing IBS in primary care; is there a role for diagnostic testing?

In current guidelines, additional investigations for diagnosing IBS are only recommended in case of alarm symptoms (weight loss, rectal bleeding, nocturnal symptoms or anaemia), poor therapeutic response, and persistent diarrhoea.(3) However, our survey demonstrated that - although most GPs agree that IBS should be a positive diagnosis - half of the patients consulting for IBS-like complaints expected diagnostic tests and specialist referral. Obviously this mismatch between the patient's expectations and the GP's approach might hamper optimal management.(1) In daily clinical practice, 15% of the IBS patients in primary care is tested, either with in-practice diagnostic tests (5%) or with endoscopy (10%).(4) Studies have shown that an extensive diagnostic work-up in patients suspected of IBS is of very limited value in terms of identification of organic disease. In large series of patients suspected of IBS laboratory tests showed thyroid dysfunction in 6%, while with routine lower gastrointestinal (GI) endoscopy abnormalities were found in only 2%.(5). IBS is a chronic disorder, with 88% of the patients remaining symptomatic after 8 years of follow-up.(6) Only in a very small subset of patients diagnosed with IBS in primary care an organic explanation is found at repeat consultations. So far, routine testing for colon cancer, coeliac disease or other possible organic diagnoses in IBS patients has not been proven to be cost-effective.(7) These observations support the recommendation to limit the diagnostic workup, and let the diagnostic process be primarily directed by IBS-like symptoms

and additional patient characteristics. Only in patients with diarrhoea there may be a need for additional diagnostic tests to differentiate irritable bowel syndrome from inflammatory bowel disorder (IBD). So far, this is mainly done by endoscopy, but in the near future patient tests for fecal biomarkers, such as calprotetine and lactoferrine, may be used to preselect patients for endoscopy.(8)

Management of IBS; which way to go?

The majority (90%) of the patients with IBS is managed in primary care, and - given the low referral rate and the results of our survey - the outcome of primary care management seems favourable for most of these.(9) Primarily, successful IBS management depends on a confident diagnosis and an open and strong doctor-patient relationship. In clinical practice GPs' management of IBS starts with exploring the patients perception and expectations. Counselling and reassurance is the next step, explaining pathophysiology and symptom generation of IBS, and the prognosis and benign background of the syndrome. Finally therapeutic options are discussed, highlighting the poor results of present drug therapy, and the need for lifestyle adaptation. Dietary advice is part of this, mainly focussing on the addition of bran to the diet. In our survey in current primary care practice more than half of the GPs starts IBS management with pharmacotherapy.(1) The majority of patients (67%) receives bulking agents on prescription i.e. the soluble fibre psyllium.(10)

What is the evidence base for dietary interventions in IBS?

A general lifestyle advice "eat more fibres in your meal" as presently practised by many primary care physicians – is not always effective and might even worsen IBS symptoms.(11) Dietary fibres primarily modulate the gut transit by increasing the bulk of the fecal mass and improving stool frequency. For that reason fibre therapy is effective in constipation. In addition fibre also affects visceral hypersensitivity and may be beneficial in IBS, through pain relief and improvement of stool frequency. Noteworthy, the fibre related recommendations in current guidelines do not differentiate between soluble (psyllium) and insoluble fibre (bran).(3;12) We demonstrated psyllium to be more effective in patients with IBS than placebo in providing adequate relief of abdominal pain or discomfort. In contrast, insoluble fibre (bran) showed no clinically relevant benefit, while many patients appear to be intolerant for bran. Based on these results adaptation of the current IBS guideline seems necessary, with a recommendation to try soluble fibre for symptom relief.

Symptom-based pharmacotherapy for IBS; any effective options left?

In many IBS patients antispasmodic agents such as mebeverine or butylscopolamine may temporarily alleviate pain.(13) However, in the Netherlands only mebeverine

(Duspatal®) is registered for the treatment of IBS. Noteworthy its effectiveness in relieving IBS symptoms has never been established in a RCT. There is some evidence for the efficacy of butylscopolamine but this drug may worsen constipation through its anticholinergic effects.(13) Therefore IBS patients with pain are probably better off taking over the counter analgesics such as paracetamol. The effectiveness of probiotics and herbal therapy in IBS, though increasingly advocated in the absence of other pharmacotherapeutic options, is not yet firmly established.(14)

Because of the high prevalence of psychiatric comorbidity, many clinicians use antidepressant drugs in IBS patients, even though their effectiveness has not been shown.(13) Evidently, IBS patients with a properly diagnosed clinical depression or anxiety disorder should be treated adequately, e.g. with antidepressants. However, these drugs mainly work in the central and not in the peripheral nervous system of the GI tract, and their effectiveness in relieving IBS symptoms has not been demonstrated. Many IBS patients who do respond to antidepressants may in fact suffer from intestinal side effects of tricyclic antidepressivants (constipation) and selective serotonine re-uptake inhibitors (diarrheoa).(15)

Novel serotonine-mediated drug therapies such as alosetron and tegaserod initially provided promising results, especially in women with predominant diarrhoea or constipation, respectively.(16;17) Both drugs, however, had a limited additional effect compared to placebo, and the relevance of their clinical application was questioned. In addition, serotonine-related drugs showed a high prevalence of adverse effects, up to 40% of the patients reported constipation or diarrhoea. Moreover, alosetron was associated with an increased risk of ischemic colitis, while tegaserod has been associated with serious cardiovascular side effects, including myocardial infarction, unstable angina, and stroke. For these reasons presently no serotonine based drugs are available for clinical treatment of IBS.

IBS treatment; are psychological interventions the ultimate solution?

Coping with their abdominal complaints is a major problem for many IBS patients. Multiple factors contribute to failing coping strategies: stressful major life events, additional somatic complaints, catastrophizing thoughts (e.g. signs of pain will ruin my day), excessive concerns, refractory symptoms and excessive impairment of daily functioning. Rationalising disease perception, reinforcing coping strategies and diminishing stress and concern are effective interventions to diminish the impact of IBS on daily life.(18) Cognitive behavioural therapy (CBT), interpersonal psychotherapy, hypnosis and relaxation/stress management are possibly effective in improving IBS symptoms and/or quality of life.(19;20) The term possibly is used here, because the methodology of most studies is suboptimal and the sustainability

of effects is unclear.(21) The psychological treatment of choice for each individual patient depends on the patient's background, their preference, the availability of services, and costs. At present the availability of services and the number of trained therapist is limited. Nurse-delivered psychological interventions, such as problem solving therapy and CBT, may facilitate wider implementation of these interventions in primary care.

Summarising; an optimal approach to IBS in primary care

IBS can be adequately diagnosed in primary care, basically by using symptoms and the patients' profile only. Additional diagnostic testing to exclude organic bowel disease, e.g. by endoscopy, is required for a small subgroup of patients only, i.e. those with either alarming or persisting symptoms. Counselling is important to ensure that the disease perception of the patient is rational, and matches that of the physician. The results of drug therapy aimed at abdominal symptom relief are generally disappointing. In contrast, the addition of soluble fibre to the daily diet causes effective symptom reduction in many IBS patients. For patients with refractory symptoms, psychological treatment or psychotropic drugs could be considered.

IBS research design and outcome issues

In functional disorder research, methodological challenges need to be met that require special attention during trial design and data analysis. A number of these issues we had to deal with in our randomised trial will be discussed briefly.

Heterogeneity in the patient population may hamper the applicability of trial results. Differences in disease characteristics such as symptom severity might influence the outcome of the intervention under study if these characteristics modify the intervention's effect on the outcome. Patients with more severe abdominal pain may have higher expectations from treatment than those who did not give informed consent. Also patients with somatic and psychiatric comorbidity may be more resistant to therapy.(22) The key issue to judge the representativeness of the trial population in clinical research is to assess whether the, inherently, selective recruitment of patients for participation in the RCT created a study population that differs essentially from the patient population encountered in daily clinical care. Indeed, our study population did differ in symptom severity from the primary care IBS population. At baseline the three treatment groups were comparable with the exception of a somewhat lower symptom severity in the psyllium group. However,

adjustment for baseline symptom severity in the multivariate analysis only increased the observed beneficial effect.
Compared to somatic disease the placebo response in functional disease is much higher (on average 40%) which makes it more difficult to demonstrate the superior effect of new treatments in clinical research.(23) As expected, many IBS patients in our trial report beneficial effects while receiving placebo.
Functional disorders are defined by subjective symptoms, and outcome assessment can often only be assessed by means of rather subjective measurements. We used the adequate relief question (of abdominal pain or discomfort), and recommend this as the preferred primary endpoint in clinical trials on functional disorders. Secondary outcomes, such as integrated symptom and quality of life measurements should be included in trials to support the clinical relevance of the results by showing concordance with the primary outcome.(24)

Future clinical research

In this thesis some new pieces were added to the jig saw puzzle known as IBS, but there is still a lot to be learned about this disorder. Many issues in IBS are not yet supported by scientific evidence, and further research is necessary to provide a stronger fundament for management guidelines in primary care.

In our view, this research should focus on 3 themes:

1. Diagnostic research
- We concluded that GPs do not use the Rome diagnostic criteria, and suggested that - in addition to symptoms - the patient's profile plays an import role in the diagnosis of IBS in primary care. Detailed analysis and validation of these criteria in future diagnostic research is required to support the diagnostic process of IBS in primary care.
- Efficient discrimination between an organic and a functional background is the core of the diagnostic process in abdominal complaints in primary care. Faecal biomarkers of inflammation may play an important role in facilitating this process. The contribution of in practice calprotectine and lactoferrine tests in ruling out organic bowel disorders in patients with IBS like complaints needs to be assessed in future research.

2. Aetiological research
- More insight is required in the profile of IBS patients in terms of potential underlying causes, disease history, comorbidity, and disease impact. This will make it possible to identify subgroups of patients, e.g. those with a

predominantly somatic comorbidity and those IBS patients with a mainly psychosocial disease burden, who may benefit from targeted interventions.

3. Therapeutic research

- The benefit from other dietary interventions, such as probiotics, needs to be addressed in high quality research. Our trial on the effects of fibre shows that such trials are indeed feasible.
- Many physicians advocate increased physical exercise as an effective stimulus for bowel activity and an easy intervention to reduce IBS complaints. The evidence base for this recommendation needs to be established in a properly designed trial.

References

1. Bijkerk CJ, de Wit NJ, Stalman WA, Knottnerus JA, Hoes AW, Muris JW. Irritable bowel syndrome in primary care: the patients' and doctors' views on symptoms, etiology and management. Can J Gastroenterol 2003 Jun;17(6):363-8.
2. Rubin G, de WN, Meineche-Schmidt V, Seifert B, Hall N, Hungin P. The diagnosis of IBS in primary care: consensus development using nominal group technique. Fam Pract 2006 Dec;23(6):687-92.
3. Jones J, Boorman J, Cann P, Forbes A, Gomborone J, Heaton K, et al. British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. Gut 2000 Nov;47 Suppl 2:ii1-19.
4. de Wit NJ, van der Wind D, Schellevis FG, van der Horst HE. Epidemiology and clinical management of irritable bowel syndrome in primary care; one year results from a nationwide database. Gut Suppl III 56, A40. 2007.
5. Hamm LR, Sorrells SC, Harding JP, Northcutt AR, Heath AT, Kapke GF, et al. Additional investigations fail to alter the diagnosis of irritable bowel syndrome in subjects fulfilling the Rome criteria. Am J Gastroenterol 1999 May;94(5):1279-82.
6. Thompson WG. The treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2002 Aug;16(8):1395-406.
7. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006 Apr;130(5):1480-91.
8. Costa F, Mumolo MG, Bellini M, Romano MR, Ceccarelli L, Arpe P, et al. Role of faecal calprotectin as non-invasive marker of intestinal inflammation. Dig Liver Dis 2003 Sep;35(9):642-7.
9. Oberndorff-Klein Woolthuis AH, Brummer RJ, de Wit NJ, Muris JW, Stockbrugger RW. Irritable bowel syndrome in general practice: an overview. Scand J Gastroenterol Suppl 2004;(241):17-22.
10. Cardol M, van Dijk L, de Jong JD, de Bakker DH, Westert GP. Tweede Nationale Studie naar ziekten en verrichtingen in de huisartspraktijk. Huisartsenzorg: wat doet de poortwachter? Utrecht/Bilthoven: NIVEL/RIVM; 2004.
11. Bijkerk CJ, Muris JW, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. Aliment Pharmacol Ther 2004 Feb 1;19(3):245-51.
12. Boukes FS, van der Horst HE, Assendelft WJ. (Summary of The Dutch College of General Practitioners' 'Irritable bowel syndrome' standard). Ned Tijdschr Geneeskd 2002 Apr 27;146(17):799-802.

13. Quartero AO, Meineche-Schmidt V, Muris J, Rubin G, de WN. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev 2005;(2):CD003460.
14. Hussain Z, Quigley EM. Systematic review: Complementary and alternative medicine in the irritable bowel syndrome. Aliment Pharmacol Ther 2006 Feb 15;23(4):465-71.
15. North CS, Hong BA, Alpers DH. Relationship of functional gastrointestinal disorders and psychiatric disorders: implications for treatment. World J Gastroenterol 2007 Apr 14;13(14):2020-7.
16. Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. Lancet 2000 Mar 25;355(9209):1035-40.
17. Tack J, Muller-Lissner S, Bytzer P, Corinaldesi R, Chang L, Viegas A, et al. A randomised controlled trial assessing the efficacy and safety of repeated tegaserod therapy in women with irritable bowel syndrome with constipation. Gut 2005 Dec;54(12):1707-13.
18. van der Horst HE, Schellevis FG, van Eijk JT, Bleijenberg G. Managing patients with irritable bowel syndrome in general practice. How to promote and reinforce self-care activities. Patient Educ Couns 1998 Oct;35(2):149-56.
19. Kennedy T, Jones R, Darnley S, Seed P, Wessely S, Chalder T. Cognitive behaviour therapy in addition to antispasmodic treatment for irritable bowel syndrome in primary care: randomised controlled trial. BMJ 2005 Aug 20;331(7514):435.
20. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. Lancet 1984 Dec 1;2(8414):1232-4.
21. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology 2002 Dec;123(6):2108-31.
22. Guthrie EA, Creed FH, Whorwell PJ, Tomenson B. Outpatients with irritable bowel syndrome: a comparison of first time and chronic attenders. Gut 1992 Mar;33(3):361-3.
23. Thompson WG. Placebos: a review of the placebo response. Am J Gastroenterol 2000 Jul;95(7):1637-43.
24. Bijkerk CJ, de Wit NJ, Muris JW, Jones RH, Knottnerus JA, Hoes AW. Outcome measures in irritable bowel syndrome: comparison of psychometric and methodological characteristics. Am J Gastroenterol 2003 Jan;98(1):122-7.

Summary

Summary

CHAPTER 1. Irritable bowel syndrome (IBS) is a functional bowel disorder in which abdominal pain or discomfort is associated with a change in bowel habit, or with features of disordered defecation. IBS is a common disorder in primary care and patients have high consultation rates, both for IBS as well as other symptoms. Although many pathophysiological explanations have been suggested for IBS, no unique mechanism has been identified. Rather it seems that the same mechanisms are responsible for abdominal pain and altered bowel habits in people with and without IBS. IBS can best be explained using a bio-psychosocial model. In general treatment of IBS should be based on the nature and severity of symptoms and the degree of psychological disturbance and functional impairment. In the management of IBS the majority of the general practitioners (GPs) provide dietary lifestyle advices, mainly focussing on increasing the fibre content of the daily diet by adding insoluble fibre (bran). In addition the majority of the IBS patients receives pharmacotherapy, frequently including bulking agents, in particular psyllium-supplements. The efficicay of dietary interventions in IBS, however, has not yet been established in prospective research. We designed and performed a randomised controlled trial (RCT) studying the effectiveness of soluble (psyllium) and insoluble fibre (bran) in primary care IBS patients. While conducting this trial several methodological challenges had to be met regarding optimal outcome measurement and patient selection.

CHAPTER 2. In order to facilitate the development of clinical guidelines and to focus future IBS research, insight into the perceptions of patients and GPs regarding IBS is required. We compared patients' and GPs' views on the symptomatology, aetiology, and treatment of IBS in a questionnaire survey. Although all patients were diagnosed by their GP as having IBS, only 18% fulfilled the Rome II criteria for IBS and 62% the Manning criteria. In both the patients' and doctors' views, IBS is related to food and stress. Initial management of IBS by the GPs starts with dietary advice (94%), counselling (77%), and drug therapy (55%). A majority of the patients did report therapeutic gain from pharmacotherapy and less from dietary interventions. Patients and GPs agree on IBS symptomatology, as outlined in the Manning criteria. Although GPs and patients consider diet and stress as important aetiological factors, pharmacotherapy remains the cornerstone of IBS management in primary care patients.

CHAPTER 3. Only a minority of patients consult a physician for IBS-like symptoms. We aimed to identify determinants of consulting behaviour in primary

care IBS patients by comparing those who consulted frequently to those who did not. In a random sample of 214 primary care IBS patients participating in a questionnaire survey we compared demographic, and disease-specific data of frequently and non frequenty consulting IBS patients. Half of the patients (44%, n=94) were frequent consulters (more than once in the preceding year) and 120 did not consult their general practitioner (GP) during the previous year or consulted the GP only once. Patients with severe IBS related abdominal pain (mean VAS score: 52.6 (scale 0-100)) and impaired health-related quality of life (mean score 76.4 (scale 0-100)) more frequently attended their GP as did patients with distress, somatisation or depression. Independent predictors of frequent consultation were the presence of Rome II defined IBS (OR 2.96 (95%CI: 1.19-5.98)), severity of abdominal pain (OR 1.03 (95%CI: 1.02-1.95)), and referral to secondary care in the preceding 2 years (OR 5.70, 95%CI: 1.20-27.0)). Consultation patterns for IBS in primary care vary considerably and are mainly driven by IBS symptomatology and symptom severity.

CHAPTER 4. Although a high prevalence of comorbidity has been reported in IBS, the historical relationship between IBS and comorbidity has not been studied. We assessed the temporal relation between IBS and clustered somatic, functional, psychiatric and psychosocial comorbidity over a 10-year time period (1996-2005) in IBS patients and matched controls. We performed a retrospective follow-up study in a large academic primary care network, comparing a random sample of 371 IBS patients with 411 age, sex and primary care practice-matched controls. All types of comorbidity were more frequently registrated among IBS patients (68% females, mean age 40, SD 13) compared to controls. Somatic disorders were highly prevalent among all patients, but more common among IBS patients than controls (OR 2.04 (95%CI: 1.48-2.81)). The highest odds ratio was found for functional disorders among in IBS patients (OR 6.64 (95%CI: 3.21-13.7)). The prevalence of somatic disorders increased six fold in the year of that IBS was diagnosed, but dropped again afterwards. The prevalence of functional, psychiatric and psychosocial problems doubled in the year of the diagnosis of IBS but remained on that level in the years after the diagnosis. Patients with different types of comorbidity might need different, targeted treatment approaches.

CHAPTER 5. Although there is growing interest in IBS research, there is as yet no consensus regarding the preferred outcome measure. We evaluated and compared the validity and appropriateness of currently available IBS outcome measures. In a panel evaluation, six reviewers independently rated, according to predetermined psychometric and methodological validation criteria, five IBS symptom scales and

five IBS health-related quality of life (HRQOL) instruments. Two of the symptom scales were rated as "good". The adequate relief of abdominal pain or discomfort question scored best. This scale demonstrates responsiveness, face-, and construct validity, and its score was considered easy to interpret and appropriate for use. According to the reviewers, the IBS Severity Scoring System performed well with regard to psychometric capacities, but its practical utility was considered debatable. The properties of the other three symptom scales were suboptimal. The practical utility of the five IBS-specific HRQOL scales was considered poor. However, the reviewers agreed that, at present, the IBS Quality of Life measurement is the best choice, since it has been most extensively validated and shows appropriate psychometric quality. We suggested the adequate relief question as the measure of first choice when assessing global symptomatology as an outcome in IBS studies. For a more detailed IBS symptom assessment the IBS Severity Scoring System is preferable. Finally, the IBS Quality of Life measurement can be used to establish changes in health-related quality of life.

CHAPTER 6. The recruitment process may generate a selected patient sample, which may threaten the generalisability of trial results. This risk is particularly high in case disease and patient characteristics demonstrate a wide variation, such as in IBS. In a randomised clinical trial assessing the effcicacy of fibre therapy in IBS we compared patients randomised (RP, n=193), non-randomised but eligible patients (NREP, n=371) and non eligible patients (NEP, n=724). Of the 2100 IBS patients, 1288 (61%) returned the questionnaire. Randomised patients had a higher intensity of IBS abdominal pain, a higher consultation rate and a longer IBS disease history compared to the other groups. Non eligible patients had less active IBS symptoms. Randomised patients do differ from those non-randomised in IBS disease characteristics. These observations may have implications for the applicability of our research outcome.

CHAPTER 7. Both dietary advice and bulking agent prescription are very common in IBS management, but the evidence for its effecicy is unclear. We performed a systematic review and aimed to quantify the effect of different types of fibre on global and symptom relief from IBS. We conducted a structured literature search in MEDLINE (1966-2002), and selected randomised controlled trials involving IBS patients treated with fibres. Analyses were done for the total group and for soluble and insoluble fibres separately. Seventeen studies were included in the analysis. None of them investigated primary care IBS patients. The methodological quality of the studies was poor. Fibre in general, is effective in the relief of global IBS symptoms (RR 1.33 (95%CI: 1.19-1.50)). IBS patients with constipation might

benefit from fibre treatment (RR 1.56 (95%CI: 1.21-2.02)), while there is no evidence that fibre is effective in the relief of abdominal pain in IBS. Soluble fibre (psyllium, ispaghula, calcium polycarbophil) showed significant improvement (RR 1.55 (95%CI: 1.35-1.78)), while insoluble fibre (corn, wheat bran) did not show significant differences compared to placebo (RR 0.89 (95%CI: 0.72-1.11)). Soluble and insoluble fibres may have different effects on IBS symptoms. Well designed clinical trials, evaluating the effect and tolerability of fibre therapy in clinically relevant patient domains, including primary care, are needed.

CHAPTER 8. We assessed the effectiveness of soluble (psyllium) or insoluble fibre (bran) in a randomised, placebo controlled trial among 275 IBS primary care patients. Patients were randomly allocated to 12 weeks treatment with either 10 grams of soluble fibre (psyllium) (n=85), 10 grams of insoluble fibre (bran) (n=97) or 10 grams of placebo (rice flour) (n=93). Statistical analyses were based on the intention-to-treat principle. A worst-case analysis was performed to deal with loss-to-follow-up. The proportion of patients with adequate relief of abdominal pain (primary endpoint) was significantly greater in the psyllium group than in the placebo group, both after 1 month (57.0% v 34.6%; RR 1.60 (95%CI: 1.13-2.26)) and 2 months of treatment (59.0% v 41.0%; RR 1.44 (95%CI: 1.02-2.06)). During the third month the difference between psyllium and placebo (46.3% v 32.1%) was no longer statistically significant (RR 1.36 (95%CI: 0.90-2.04)). The results of the worst case-analysis were simular. Bran was more effective as compared to placebo after 3 months of treatment only (32.0% v 19.4%; RR 1.70 (95%CI: 1.12-2.57)) but this was no longer statistically significant in the worst case analysis (RR 1.45 (95%CI: 0.97-2.16)). After 3 months of treatment the mean symptom severity reduction in the psyllium group was 90 points, versus 49 points in the placebo group (p=0.03). No differences were found with respect to quality of life in the three groups. We conclude that psyllium therapy offers benefit in IBS patients, wheras bran should only be recommended with caution.

CHAPTER 9. In the general discussion we discussed the main outcomes of the studies presented in this thesis, provided recommendations for management of patients with IBS in primary care and suggested directions for future research. In clinical practice GPs' management of IBS should start with exploring the patient's perception and expectations. Counselling and reassurance is the next step, explaining the benign background of the syndrome. Dietary advice is one of the therapeutic options, and based on the outcome of our research we recommend to try soluble fibre for symptom relief. In functional disorder research special attention should be paid to methodological issues around trial design including placebo

response, outcome assessment and patient selection as these are critical determinants of valid functional disorder research. Future research should focus on diagnostic issues (the role of diagnostic criteria and the value of novel diagnostic tests), aetiological background of IBS (disease history, comorbidity, and disease impact) and therapeutic issues (the efficicay of probiotics, and physical exercise).

Samenvatting

Samenvatting

HOOFDSTUK 1. Het prikkelbare darm syndroom (PDS) is een functionele buikaandoening die geassocieerd wordt met een veranderd ontlastingspatroon, of met kenmerken van een verstoorde ontlasting. PDS is een veel voorkomende aandoening in de huisartsenpraktijk en patiënten hebben een hoge consultatie frequentie, zowel voor PDS als voor andere symptomen. Hoewel veel pathosfysiologische verklaringen voor PDS zijn aangedragen is er geen uniek mechanisme aangetoond. Eerder lijkt het erop dat dezelfde mechanismen verantwoordelijk zijn voor buikpijn en veranderd ontlastingspatroon bij mensen met en zonder PDS. PDS kan het beste verklaard worden door gebruik te maken van het bio-psychosociale model. De algemene behandeling van PDS dient gebaseerd te zijn op de aard en ernst van de symptomen, de mate van psychologische ontregeling en functionele beperking. Bij de behandeling van PDS geeft de meerderheid van de huisartsen dieetadviezen, vooral gericht op het verhogen van het vezelgehalte in de voeding door het toevoegen van onoplosbare vezels (tarwezemelen). Aanvullend krijgt de meerderheid van de patiënten met PDS medicamenteuze behandeling, m.n. bulkvormers, in het bijzonder psyllium supplementen. De effectiviteit van dieet interventies bij PDS is echter nog niet vastgesteld in prospectief onderzoek. Wij hebben een een gerandomiseerd gecontroleerd onderzoek (RCT) opgezet en uitgevoerd om de effectiviteit van oplosbare vezels (psyllium) en onoplosbare vezels (tarwezemelen) bij patiënten met PDS in de huisartsenpraktijk te onderzoeken. Bij het uitvoeren van dit onderzoek werden verschillende methodologische problemen met betrekking tot het bepalen van de optimale uitkomstmaat en patiëntenselectie onderzocht.

HOOFDSTUK 2. Om de ontwikkeling van klinische richtlijnen te ondersteunen en te richten op PDS onderzoek is het noodzakelijk inzicht te krijgen in de beleving van patiënten en huisartsen ten opzichte van PDS. We vergeleken de mening van patiënten en huisartsen op het gebied van symptomen, etiologie en behandeling van PDS. Hoewel alle patiënten door hun huisarts waren gediagnosticeerd met PDS voldeed slechts 18% aan de Rome II criteria en 62% aan de Manning criteria. Patiënten en huisartsen zijn van mening dat PDS is gerelateerd aan voeding en stress. Huisartsen starten de behandeling van PDS in 94% van de gevallen met dieetadvies, 77% met voorlichting en 55% met medicamenteuze behandeling. De meerderheid van de patiënten verklaard baat te hebben bij medicamenteuze behandeling en in mindere mate van dieetinterventies. Patiënten en huisartsen hebben overeenstemming over de PDS symptomen, zoals omschreven in de Manning criteria. Hoewel dieet en stress door huisartsen en patiënten als belangrijke

etiologische factoren worden gezien, blijkt medicamenteuze behandeling het uitgangspunt voor de behandeling van PDS in de huisartsenpraktijk.

HOOFDSTUK 3. Slechts een minderheid van de patienten consulteren een arts voor PDS symptomen. Het doel van dit onderzoek was om determinanten te bepalen voor het consultgedrag van PDS patienten in de huisartsenpraktijk. Een willekeurige steekproef - van 214 PDS patienten - werd uitgenodigd voor deelname aan een enquêteonderzoek. We vergeleken de demografische en ziektespecifieke kenmerken en gegevens van patiënten die frequent en niet frequent consulteerden voor PDS. De helft van de patiënten (44%, n=94) waren patiënten die frequent het spreekuur bezochten (meer dan eens in het voorgaande jaar) en 120 patiënten hadden hun huisarts niet bezocht in het voorgaande jaar of slechts een keer. Patiënten met ernstige PDS gerelateerde buikklachten (gemiddelde VAS: 52.6 (schaal 0-100)) en verminderde ziektespecifieke kwaliteit van leven (gemiddelde score: 76.4 (schaal 0-100)) bezochten vaker hun huisarts dan patiënten met stress, somatisatie of depressie. Onafhankelijke voorspellers voor frequent huisartsenbezoek waren de aanwezigheid van Rome II gedefinïeerde PDS (OR: 2.96 (95%CI: 1.19-5.98)), ernst van de buikklachten (OR 1.03 (95%CI: 1.02-1.95)) en de patiënten die de afgelopen 2 jaar verwezen waren naar de tweedelijn (OR 5.70 (95%CI: 1.20-27.0)). De consultpatronen voor PDS in de huisartsenpraktijk variëren aanzienlijk en worden vooral bepaald door de symptomatologie en ernst van PDS symptomen.

HOOFDSTUK 4. Hoewel comorbiditeit veel voorkomt bij PDS is de tijdsrelatie tussen PDS en comorbiditeit niet duidelijk. We onderzochten het historisch perspectief tussen PDS en geclusterde somatische, functionele, psychiatrische en psychosociale comorbiditeit over een periode van 10 jaar (1996-2005) bij PDS patiënten en gematchte controles. In een retrospectief follow-up onderzoek vergeleken we in een academisch netwerk van huisartsenpraktijken (HNU) 371 PDS patiënten en 411 controles het voorkomen van comorbiditeit. PDS patiënten (68% vrouwen, gemiddelde leeftijd 40 jaar (SD 13) hadden in vergelijking met controles over alle clusters meer comorbiditeit. Somatische aandoeningen komen veel voor, maar zijn meer uitgesproken bij PDS patiënten (OR 2.04 (95%CI: 1.48-2.81)). Bij PDS patiënten werden de hoogste odds ratios gevonden voor functionele aandoeningen (OR 6.64 (95%CI: 3.21-13.7)). Somatische aandoeningen hadden een hoge prevalentie bij patiënten met een korte historie van PDS (<2 jaar) en hadden een zesvoudige piek in het jaar dat de PDS diagnose werd gesteld. De prevalentie van functionele, psychiatrische en psychosociale problemen verdubbelde in het jaar van de PDS diagnose en bleef op dat niveau in de jaren na de diagnose. Patiënten

met verschillende typen van comorbiditeit hebben mogelijk baat bij een gerichte behandelbenadering.

HOOFDSTUK 5. Hoewel er meer aandacht is voor PDS onderzoek is er geen consensus over de optimale uitkomstmaat. We evalueerden en vergeleken de validiteit en toepasbaarheid van de huidige beschikbare PDS uitkomstmaten. In een panel van zes reviewers werden onafhankelijk van elkaar op basis van vooraf vastgestelde psychometrische en methodologische validiteitcriteria vijf PDS symptoom schalen en vijf PDS ziektespecifieke kwaliteit-van-leven instrumenten gescoord. Twee van de symptoom uitkomstmaten scoorden goed. De adequate reflief of abdominal pain or discomfort scoorde het beste. Deze score was responsief, valide en werd beschouwd als eenvoudig te interpreteren en geschikt voor gebruik in de dagelijkse praktijk. Volgens de reviewers voldeed de IBS Severity Scoring System met betrekking tot de psychometische kwaliteit, echter de praktische toepasbaarheid werd als twijfelachtig beoordeeld. De kenmerken van de andere symptoom scores werden als suboptimaal beschouwd. De PDS ziektespecifieke kwaliteit-van-leven vragenlijsten scoorden slecht op hun praktische toepasbaarheid. De IBS Quality of Life measurement is de beste keuze, deze score is het meest valide en toont een goede psychometrische kwaliteit. De adequate relief vragenlijst is de uitkomstmaat van voorkeur in PDS onderzoek om verandering in globale symptomen te meten. Voor het meten van gedetailleerde symptomen is de IBS Severity Scoring System te prefereren. Tenslotte, PDS ziektespecifieke kwaliteit-van-leven instrumenten zijn nog onvoldoende geschikt om als primaire uitkomstmaat te gebruiken.

HOOFDSTUK 6. Het wervingsproces van patiënten voor een onderzoek kan de generaliseerbaarheid van de onderzoeksresultaten beïnvloeden. Dit is met name het geval als ziekte- en patiëntkenmerken veel variatie vertonen zoals bij PDS. In een gerandomiseerd gecontroleerd onderzoek naar de effectiviteit van vezels bij PDS vergeleken we patiënten gerandomiseerd (RP, n= 193), niet-gerandomiseerd maar geschikte patiënten (NREP, n=371) en patiënten niet geschikt voor deelname (NP, n=724). Van de 2100 uitgenodigde patiënten retourneerden 1288 (61%) de vragenlijst. Gerandomiseerde patiënten hadden ernstigere PDS gerelateerde buikpijn, consulteerden vaker en hadden een langere PDS ziektegeschiedenis in vergelijking met de andere groepen. Niet geschikte patiënten werden vooral geëxcludeerd in verband met de afwezigheid van actieve PDS symptomen. Gerandomiseerde en niet-gerandomiseerde patiënten verschillen in de PDS gerelateerde ziektekenmerken. Deze observaties hebben mogelijk implicaties voor de toepasbaarheid van onze onderzoeksuitkomsten.

HOOFDSTUK 7. Bij de behandeling van PDS komt zowel het advies meer vezels te gebruiken als het voorschrijven van bulkvormers veel voor, het bewijs voor de effectiviteit van deze behandelingen zijn echter onduidelijk. Met behulp van een systematische zoekopdracht werd gezocht naar gerandomiseerd onderzoek over de behandeling van PDS patiënten met vezels en had het doel het effect van verschillende typen vezels op globale- en specifieke symptoomvermindering te kwantificeren. We hebben een gestructureerd literatuur onderzoek in MEDLINE (1966-2002) opgezet en selecteerden gerandomiseerd gecontroleerd onderzoek bij PDS patiënten behandeld met vezels. Analyses werden uitgevoerd voor de totale groep en patiënten behandeld met oplosbare en onoplosbare vezels. Zeventien studies werden geïncludeerd in de analyse. Geen van de onderzoeken had patiënten uit de huisartsenpraktijk ingesloten. De methodologische kwaliteit van de onderzoeken was slecht. Na pooling van de onderzoeksgegevens bleken vezels effectief voor de behandeling van algemene PDS symptomen (RR 1.33 (95% CI: 1.19-1.50)) en PDS gerelateerde obstipatie (RR 1.56 (95%CI 1.21-2.02)), er is geen bewijs dat vezels effectief zijn bij de behandeling van buikpijn bij PDS. Oplosbare vezels (psylliumzaad, ispaghula, calcium polycarbophil) zijn effectief bij de behandeling van globale PDS symptomen (RR 1.55 (95%CI: 1.35-1.78)), terwijl onoplosbare vezels (tarwezemelen) niet effectief zijn (RR 0.89 (95%CI: 0.72-1.11)). Oplosbare en onoplosbare vezels hebben een verschillend effect op PDS symptomen. Goed opgezet klinisch onderzoek is noodzakelijk om het effect en bijwerkingen van vezels bij de behandeling van PDS te beoordelen.

HOOFDSTUK 8. We onderzochten het effect van oplosbare (psyllium) en onoplosbare (tarwezemelen) vezels in een gerandomiseerd gecontroleerd onderzoek (RCT) bij 275 PDS patiënten in de huisartsenpraktijk. Patiënten werden willekeurig toegewezen aan behandeling van 12 weken met 10 gram oplosbare vezels (psyllium) (n=85), 10 gram onoplosbare vezels (tarwezemelen) (n=97) of 10 gram placebo (rijstebloem) (n=93). De analyses waren op basis van intention-to-treat principe. Een worst-case analyse werd uitgevoerd om met de uitgevallen patiënten om te gaan. De proportie van patiënten met adequate vermindering van buikpijn of ongemak (primaire eindpunt) was groter in de psylliumgroep dan in de placebogroep, zowel na 1 maand (57.0% vs 34.6%; RR 1.60 (95%CI: 1.13-2.26)) en 2 maanden (59.0% vs 41.0%, RR 1.44 (95%CI: 1.02-2.06)). Het verschil tussen psyllium en placebo (46.3% vs 32.1%) was gedurende de derde maand niet statistisch significant (RR 1.36, (95%CI: 0.90-2.04). De resulaten in de worst-case analyse waren gelijk. Tarwezemelen waren pas na 3 maanden behandeling meer effectief in vergelijking tot placebo (32.0% vs 19.4%, RR 1.70 (95%CI: 1.12-2.57)), maar dit was niet langer statistisch significant in de worst-case analyse (RR 1.45 (95%CI 0.79-2.16)). Na 3

maanden behandeling was de gemiddelde IBS Symptom Severity Score reductie in de psylliumgroep 90 versus 49 punten in the placebo groep (p=0.03). Er werden in de 3 groepen geen verschillen gevonden in ziektespecifieke kwaliteit van leven. We concluderen dat psyllium voordelen bied voor PDS patiënten in de huisartsenpraktijk, waar tarwezemelen met terughoudendheid moet worden geadviseerd.

HOOFDSTUK 9. In de algemene discussie bediscussieerden we de belangrijkste uitkomsten van de onderzoeken in dit proefschrift en geven aanbevelingen voor de behandeling van PDS patiënten in de huisartsenpraktijk en doen suggesties voor verder onderzoek. In de klinische praktijk zou de PDS behandeling door de huisarts moeten starten met het onderzoeken van de perceptie en verwachtingen van de patiënt. Uitleg en geruststelling is de volgende stap, waarbij de goedaardige achtergrond van het syndroom wordt uitgelegd. Dieetadvies is onderdeel van de therapeutische opties, en gebaseerd op de uitkomsten van ons onderzoek bevelen we aan om oplosbare vezels (psyllium) te gebruiken voor symptoomvermindering.
In onderzoek naar functionele aandoeningen moet er speciale aandacht zijn voor methodologische zaken rond de onderzoeksopzet: placeborespons, meten van de uitkomst en selectie van patiënten omdat dit essentiële determinanten zijn voor valide onderzoek naar functionele aandoeningen. Toekomstig onderzoek moet zich richten op: diagnostisch onderzoek (de rol diagnostische criteria en de plaats van diagnostische tests), etiologische achtergrond van PDS (ziektegeschiedenis, comorbiditeit en ziekte impact) en therapeutisch onderzoek (de effectiviteit van probiotica en lichamelijke beweging).

Dankwoord

Dankwoord

Dit proefschrift vormt de weerslag van 8 jaar werk en onderzoek op het gebied van prikkelbare darm syndroom (PDS) in de huisartsenpraktijk. In die periode heb ik veel mensen ontmoet die zich daar op eigen wijze mee bezighielden en een bijdrage leverden bij de totstandkoming van dit proefschrift. Ik wil hun allen bedanken voor hun steun, enthousiastme en begeleiding.

De oorsprong van dit proefschrift ligt in 2000. Het College voor Zorgverzerkingen (CVZ) had het Julius Centrum voor Gezondheidswetenschappen en Eerstelijnsgeneeskunde van het Universitair Medisch Centrum Utrecht en de Capaciteitsgroep huisartsgeneeskunde van de Universiteit Maastricht gevraagd om de mogelijkheid van een gerandomiseerd gecontroleerd onderzoek, gericht op dieetinterventies bij PDS in de huisartsartsenpraktijk, te onderzoeken. In de uitvoering van een dergelijk onderzoek worden drie hoofdproblemen voorzien: de keuze van de optimale uitkomstmaat, standaardisatie van het dieet en de opzet van het onderzoeksontwerp. De twee afdelingen organiseerden een conferentie met nationale en internationale experts waar de resultaten van ons onderzoek werden gepresenteerd. De participanten waren unaniem van mening dat een onderzoek naar PDS in de huisartsenpraktijk zich zou moeten richten op de effectiviteit van oplosbare en onoplosbare vezels. Ik wil de deelnemers bedanken voor hun inbreng. In 2004, na mijn voltooïng van de huisartsopleiding, kon dat gerandomiseerde onderzoek gefinancierd door ZonMw fonds ‘Alledaagse Ziekten’ van start gaan. De onderzoeken gepresenteerd in dit proefschrift zijn het resultaat van de gebundelde krachten van alle participanten in dit project.

Onderzoek doen is met vallen en opstaan, stug doorgaan en jaren bezig zijn met een onderwerp. Het was niet altijd even gemakkelijk. Mijn werk als huisarts en ook mijn privéleven kwamen vaak op de tweede en derde plaats. Ik heb het onderzoek met veel plezier gedaan, maar ik ben blij dat het afgerond is.

Alle patiënten, huisartsen, praktijkassistentes en praktijkverpleegkundigen die een bijdrage hebben geleverd aan het tot stand komen van dit proefschrift wil ik bedanken. Zonder jullie enthousiasme was het nooit mogelijk geweest om dit project uit te voeren.

Hooggeachte promoter, professor Arno Hoes. Je deur stond open en ik kon altijd met mijn vragen bij je terecht. De projectbesprekingen over de voortgang en afronding van het project vond ik erg inspirerend. Als ik het even niet meer zag

zitten, kreeg ik van jou weer inspiratie om door te kunnen gaan. Je accuratesse en schrijfvaardigheid zijn tot in detail terug te vinden in dit proefschrift.

Hooggeachte promotor, professor André Knottnerus. Ik heb bewondering voor je betrokkenheid bij het project. Ongelofelijk hoe snel je een artikel kan doorgronden en beter kan maken. Je adviezen hebben er toe geleid dat de presentatie van de resultaten werd opgekrikt.

Geachte co-promotor, dr. Niek de Wit. Je ervaring en luisterend oor zorgden ervoor mijn motivatie hoog te houden en het project goed af te ronden. Jij was het meest betrokken bij het onderzoek en we hebben veel mooie en moeilijke momenten van het onderzoek gedeeld. Planningen werden niet altijd gehaald, maar zonder problemen maakten we weer nieuwe. Ik heb veel van je geleerd; dank doorvoor.

Geachte co-promotor, dr. Jean Muris. Je bent een rustpunt in hectische tijden. De ritjes (met vezels) naar het Limburgse land heb ik met veel plezier gedaan. Je had altijd tijd om mijn vragen te beantwoorden.

Frances Verheij en later Bernard Slotboom bedankt voor het opzetten en beheren van de data van dit onderzoek. Jullie hebben een uitstekend databestand afgeleverd. Hanneke den Breeijen en Nicole Boekema, bedankt dat jullie de voortgang van het onderzoek hebben ‘gemonitored’. Peter Zuithoff, jouw statistische adviezen waren onmisbaar. De Juliuspoli: Lydeke Zwart, Lizeth Vendrig en Manja van Wezep wil ik bedanken voor hun inzet om de dataset compleet te krijgen. Kirsten Sigterman, Marieke Heubers en Feike Vleugel hebben in het kader van een wetenschappelijke stage aan dit project meegewerkt. Ik vond het leuk om jullie te begeleiden.

Collega promovendi, (oud)kamergenoten: Ineke Welschen, Birgitte van Staay, Catherine Weijnen, Frans Rutten, Wim Opstelten, Ruud Oudega, Roeland Geijer, als laatste van de ‘gang’ rond ik nu mijn proefschrift af. Rykel van Bruggen, Paul Janssen, Frits Cleveringa, Hans Kelder, Mariëlle van Avendonk, Onno van der Spoel, Tjarda Scheltens, Lidewij Broekhuizen, veel succes met afronding van jullie projecten. Allemaal bedankt voor de collegiale sfeer, liters koffie en de gesprekken bij het kopieerapparaat. De vanillegeur en dozen tot aan het plafond waren wel het hoogtepunt.

Leden van de leescommissie, prof. dr. André Smout, prof. dr. Yolanda van de Graaf, prof. dr. Henriette van der Horst, prof. dr. Peter Whorwell, bedankt dat jullie de tijd namen om mijn proefschrift te beoordelen. A special word of thanks to professor

Whorwell for his enthusiastic advice in the earlier phase of designing the trial and his willingness to travel to Utrecht to attend the defence ceremony.

Martin Voerknecht, samen zaten we in de collegebanken en ik vind het fijn dat je ook op dit moment, als mijn paranimf, aan mijn zijde staat. Veerle Jacobs bedankt dat je de praktijk wilde 'waarnemen' als ik voor overleg naar het Julius moest. Ik vind het dan ook een eer dat je mijn paranimf bent.

Ik bedank mijn collega's van de Leidsche Rijn Julius Gezondheidscentra voor hun interesse in de voortgang van het onderzoek.

Mijn familie en vrienden wil ik bedanken voor hun liefde en aandacht.

Lieve Sietske en Julian, bedankt voor jullie steun en geduld. Ik ben trots op jullie.

René Bijkerk
Utrecht, 26 februari 2008

Publications by the author

Publications by the author

Bijkerk CJ, de Wit NJ, Stalman WAB, Knottnerus JA, Hoes AW, Muris JWM. Irritable bowel syndrome in primary care, the patient's and doctor's views on symptoms, aetiology and management. *Can. J Gastroenterol.* 2003;17:363-368.

Bijkerk CJ, de Wit NJ, Muris JWM, Jones RH, Knottnerus JA, Hoes AW. Outcome measures in irritable bowel syndrome comparison of psychometric and methodological properties. *Am J Gastroenterol* 2003;98:122-7.

Bijkerk CJ, Muris JWM, Knottnerus JA, Hoes AW, de Wit NJ. Systematic review: the role of different type of fibres in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2004;19:245-251.

Bijkerk CJ, Muris JWM, Knottnerus JA, Hoes AW, de Wit NJ. Vezels zijn maar weinig effectief bij de behandeling van prikkelbaredarmsyndroom: een systematische review. *Huisarts Wet*. 2005;19:245-251

Bijkerk CJ, Muris JWM, Knottnerus JA, Hoes AW, de Wit NJ Randomised patients in irritable bowel syndrome research had different disease characteristics compared to eligible and recruited patients. *Clin J Epidemiol.* Accepted for publication.

Curriculum vitae

Curriculum vitae

René Bijkerk was born on August 8, 1972, in Steenwijkerwold, the Netherlands. He graduated from MAVO, HAVO and VWO in Steenwijk. In 1992 he attended the University of Groningen to study medicine, where he obtained his Medical Degree in 1998. During his study he was a member of the student rowing club Gyas and rowed and coached in the regional and national student league. From 1998 to 2000 he worked as an intern at the department of gastroenterology and psychiatry at the Isala Klinieken in Zwolle. In 2000/2001, he was employed at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht to perform - in collaboration with Care and Public Health Research Institute (CAPHRI), Department of General Practice, Maastricht University - a research project on the feasibility of a randomised controlled trial in primary care, focusing on therapeutic interventions in the management of iritable bowel syndrome. From 2001 until 2003, he underwent his vocational training to become a general practitioner at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht and he was vice-chairman of the Dutch National Association of General Practitioners trainees (LOVAH). In 2004 he started working as a general practitioner at the Leidsche Rijn Julius Health Center Terwijde while working part-time at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands, where he completed this thesis.

In 2004 he married and he is father of a son. He likes to cycle and enjoys reading novels.

Frequently used abbreviations

CI	confidence interval
GP	general practitioner
IBS	irritable bowel syndrome
OR	odds ratio
P	p-value
QOL	quality of life
RCT	randomised controlled trial
RD	risk difference
RR	relative risk
SD	standard deviation
VAS	visual analogue scale